THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF
THE AMERICAN TRUDEAU SOCIETY

VOLUME LIII
JANUARY-JUNE, 1946

PUBLISHED MONTHLY
AT MT. ROYAL AND GUILFORD AVENUES, BALTIMORE 2, MD.
BY THE NATIONAL TUBERCULOSIS ASSOCIATION

CONTENTS: ORIGINAL ARTICLES

Number 1, January, 1946

Number 2, February, 1946

Number 3, March, 1946

Number 6, June, 1946

"SPEED OF REACTION" HYPOTHESIS

II. Further Numerical Implications Regarding Tuberculosis

HIBBERT WINSLOW HILL[1]

This hypothesis offers, concerning all infectious diseases, that, in the course of all natural infections and reinfections, the degree of specific tissue damage attainable by any virulent immunity-eliciting pathogen is controlled, primarily and chiefly, by a single genetic item of the infectee's heredity (1, 2).

This genetic item is taken to act by determining, for each particular infectee, the length of the time interval between his reception of a given specific immunity-eliciting stimulus, natural or "artificial," and the resulting specific-immunity response of his tissues. This interval is designated as the immunity time-lag. (See table 4.)

It is obvious that the shorter this immunity time-lag (that is, the earlier in the course of any given infection such specific immunity begins to act) the less will be the damage that the infection can do, and *vice versa*.

Just so, an incipient fire may be completely extinguished by one gallon of water, if the one gallon be used early; while delay may make unavailing even thousands of gallons used later.

In the following text and tables, certain implications of the hypothesis are described as they appear to the writer. Whether or not these implications approximate the realities of tuberculosis closely enough to add to our knowledge of those realities others must judge.

Fundamental to the hypothesis are certain natural factors which can be numerically expressed as follows:

The natural unit factors of all infections (discussed here, however, chiefly in relation to tubercle).

The basic unit for all tubercle infections appears as one single living, growing and ultimately fissioning tubercle bacillus, as it exists in the living tissues during its brief individual life-span; that is, during its one fission-interval, from the fission of its parent cell, which produced it, to its own fission, which ends it.[2]

This fission-interval, as shown by the rapidly multiplying pathogens of the acute infections, is measurable in minutes; but apparently in hours when the slow-growing pathogens are concerned. It is not impossible that one typhoid bacillus may by fission (every thirty minutes or so?) become more than a million million bacilli in the time (twenty-four hours?) ordinarily required for one tubercle bacillus to become two tubercle bacilli. (Table 1—Notes.)

Fission: Each normal living tubercle bacillus which finds its milieu satisfactory grows; that is, increases its substance, hence its bulk and its weight, at the

[1] Hackensack, P. O., Minnesota.

[2] A single *dead* pathogen cell has long been the unit of dead vaccines. It is logical enough that the living, growing, fissioning pathogen cell should be the unit when the phenomena due to that life and reproduction are being considered.

expense of its milieu; and in its metabolism manufactures various specific biochemical agents, allergenic, immunogenic, pathogenic and doubtless others, specific and nonspecific.

Coming thus in a few hours to maturity and to the bulk and weight of its parent, it fissions just as its parent did some hours before, by dividing transversely into two separate living halves, each a half-length replica of its parent.

Evidently these two new short bacilli contain between them all of the living substance of their parent cell as of the moment of fission; which parent cell therefore no longer exists; having not merely produced, but *become* its two descendents. Hence no aggregation of bacilli reproduced only by fission can contain any of its lineal ancestors, living or dead; nor can any contained dead bacillus ever have had any descendents.[3]

At the moment when the two new bacilli appeared, the two together equalled their single parent in bulk; but at maturity the two together obviously are double the single parent's bulk;[4] they together have grown at an expense to their milieu double that of their single parent; and together they have manufactured double the amount of the same specific biochemical agents. But each singly is merely a replica of its parent and has produced a like quota of the same products. Hence from each one living bacillus which appears in the tissues one, and only one, quota of products would form also.

Obviously the most notable function of the bacillary unit is that of a highly specialized, very short-lived factory, which, after turning out its one quota of unique biochemical agents, disappears in the act of setting up two new similar factories. It is these products alone that affect the animal body economy specifically. Apart from these products, the bacillary unit is a "foreign particle" only.

Hence inevitably arises a second natural unit—consisting of the one quota of biochemical agents contributed by one bacillary unit during its one brief career from fission to fission.

The over-all evidence seems to point to a practical uniformity, qualitative and quantitative, in these quotas as produced by the living virulent human type tubercle bacilli usually found in human tissues. When marked over-all differences are recognized they are usually found to relate rather to the directly pathogenic elements of the quotas than to the probably more stable allergenic and immunogenic elements (for example, attenuated cultures).

The influence on the tissues of a single such quota must be infinitesimal; and, unlike the living bacilli, the quotas are incapable of self-multiplication.

[3] Human type tubercle bacilli *Mycobacterium tuberculosis* (*hominis*) branches at times. But, in the tissues of North American white infectees, fission appears as overwhelmingly the chief process of reproduction.

[4] The combined bulks of three billion tubercle bacilli may be taken as approximating 1 cubic millimeter. Should all fission, the new six billion would have at first the same 1 cubic millimeter combined bulk; but, on reaching maturity, the combined bulk of the six billion would approximate 2 cubic millimeters. (Necessarily all such calculations are illustrative rather than strictly factual.)

But the bacilli—the factories which produce one quota each—do increase by fission; and "normally" (that is, until fission-check of some sort begins) on a strict logarithmic schedule, thus: $2^0, 2^1, 2^2, 2^3, \ldots 2^n$; one bacillus thus presenting 1024 living bacilli *at* its tenth fission. (See table 1.)

But, in reaching, at fs. (fission) 10, these 1,024 existing bacilli, 1,023 bacilli (the sum of the logarithmic series from the initial one bacillus to the 512 bacilli of fs. 9) have each appeared by fission, have grown and produced each one quota, and have then disappeared by fission into a new crop of bacilli; which crop in turn has grown and produced one quota from each of its bacilli, and then has disappeared by fission into the next crop. Each crop therefore exists only during one fission-interval, but during that fission-interval constitutes all the (living) bacilli there are in that particular focus of infection, for its predecessors have disappeared by fission, and its own prospective fission-descendents have not yet appeared.

Thus arises the concept, already implied as applicable, *mutatis mutandis*, to all the infectious diseases, namely, that each new crop of bacilli produced by fission *within the tissues constitutes in effect a new infection*.

Only the initial dose of any exogenous infection or reinfection is truly exogenous. From and including the first fission to the last fission, the bacilli "and all their works," allergenic, pathogenic, immunogenic, metastatic, etc., have their immediate origins wholly within the body.

For example: Table 1, schedule *a*, fs 6, shows 64x bacilli as the total living bacillus load *at* fs. 6 of the original infection.

On fission, this 64x bacilli becomes 128x bacilli; that is, the total living bacillus load *at* fs. 7, which latter therefore shows an increase in the total living bacillus load at fs. 6 of 64x bacilli, because the total living bacilli of fs. 6 (64x) disappear in the act of fissioning, reappearing at the same instant as 128x new bacilli; thus 64x of these 128x new bacilli merely replace in number their 64x parents; the remaining 64x constituting the net increase in the total living bacillus load at fs. 7 over that at fs. 6.

If, at fs. 6, before its 64x bacilli fission, an exogenous reinfection occurs, also of 64x bacilli, the total living bacilli load at fs. 6 becomes at once 128x bacilli; which is exactly the total living bacillus load which fs. 6 by itself shows, after its fission, that is, at fs. 7.

Considering the course of an originally exogenous infection as a series of fission-crops, each derived directly from its immediate predecessor, each fission-crop presents itself as a new independent infection; each of which, excepting of course the initial dose, is necessarily of endogenous immediate origin.

Such fission-crops then constitute the only new infections of endogenous origin which actually add to the total existing living bacillus load of the tissues; for other forms of endogenous reinfections (as by metastasis, etc.) merely redistribute the existing load but do not add to it. (See table 3.) Latency, if and when it occurs, diminishes the total existing active load at the time the latency begins, by the number of the bacilli which, by developing latency, necessarily become inactive.

Hence, the fs. 10 bacillus crop consists of 1,024 living bacilli but represents

a total bacillus load to date of 2,047 bacilli (1,024 now living and 1,023 not dead but disappeared by fission). This means a total production by the infection, from the first one bacillus to fs. 10, inclusive, of 2,047 quotas of the specific biochemical agents, each containing allergenic, immunogenic and pathogenic elements. Evidently the infection load will continue to expand, following the same structural principles, unless and until fission be checked in some manner.

Fission, therefore, functions to provide only the bacillary units, which then provide the quota units; only the latter can induce damage, but also only the latter can induce immunity or allergy. Therefore, no living bacilli, no infection; no quotas, no specific results from infection. Dead bacilli, however, yield such quotas as may have been formed in them and are still contained in them at the moment of death (for example, dead vaccines).

Since 1,000 quotas may be taken to present 1,000 allergenic elements and 1,000 pathogenic elements as well as 1,000 immunogenic elements, each of the first two elements, the allergenic and the pathogenic, may also be taken as each constituting specific units; each such unit acting under the control of its own specific time-lag; both time-lags different from but analogous to that herein postulated for the immunogenic unit.

Although each of these three units (the allergenic, the pathogenic and the immunogenic) ultimately yields recognizable results from responsive tissues, respectively, allergy, pathogenesis, immunity, yet doubtless their respective time-lags have ended, and therewith these results have been initiated some time before these results become overt to our present observational facilities. This is particularly obvious regarding the immunogenic unit, the only one the quantitative value of which is herein attempted, as follows.

The third, or *immunogenic*, unit is merely one element of the quota unit. The quantitative value of this third unit does not emerge so definitely as do those of the first two (the bacillary unit and the quota unit) but the available evidence indicates that it may be safely, if tentatively, set at *just so much immunity-eliciting stimulation* as will suffice to induce (but only, of course, from responsive tissues) the fourth or actually functioning immunity unit.

The fourth, or *active immunity*, unit is then taken to be just *so much antibacterial immunity* as suffices to "quell" (or put out of action) one living mature cognate pathogen cell; hence probably, *in re* tubercle, to kill one mature living bacillus.[5]

This "quelling," in tubercle, certainly must include the stopping of fission ("bacteriostasis"), but probably is in fact bactericidal also; whether it also includes the neutralization of the allergenic or pathogenic elements of the quotas

[5] This unit value may equally well be taken as less than one bacillus or as any multiple of one, without detriment to the principles of the hypothesis; and may be taken to act on immature instead of on mature bacilli. But for illustrative purposes and as a first approximation, the one mature bacillus value is simpler and is herein always used.

seems uncertain, but this is not essential to the present discussion. (See table 4—Notes.)

This immunity unit obviously differs widely in origin, in nature, and in action from the preceding three; thus, the first three units (the bacillary, the quota and the immunogenic) are integral to the bacillary substance, for they appear wherever the bacilli flourish, whether in lifeless artificial media or in living animal tissues. Even the dead bacilli (for example, dead vaccines) may be allergenic, immunogenic and (virulent strains) pathogenic in some degree.

In strong contrast, the fourth or specific active immunity unit, if and when formed, is an animal-tissue output. But it is not integral to the animal substance; for in normal uninfected tissues it is unknown in nature from birth to death.[6] Only a *potentiality for* immunity production is integral to such tissues—a very specific potentiality which, so far as now known, can be elicited only by the administration, natural or artificial, of the very specific cognate immunogenic unit. No substitute for such specific immunogenic units has yet been found; nor can a thus specifically-stimulated response of the tissues be checked in nature except by the cessation of the specific stimulation or by the death or near death of the tissues.

That there is no direct correlation between "health" and immunity-production or action would therefore seem rather evident; for not only are healthy tissues, unless specifically stimulated, quite incapable of developing immunity, but also it is precisely during periods of "depressed vitality," such as evidenced by the fever, malaise, malnutrition, dysfunction, pain, etc., of a specific infectious disease, that specific immunity units chiefly develop; and usually in such quantities that not only is the current infection quelled (by "concurrent-immunity"), but also a huge surplus of immunity units is left over ("free immunity"), capable of offsetting later cognate infections.

Such surplus, protective "free immunities" may last throughout subsequent life (smallpox, chickenpox, measles, poliomyelitis, etc.); or for a few years (vaccinia, diphtheria, typhoid, etc.); or for a few weeks only ("colds"). The evidence regarding the duration of protection against further tubercle infection which may be conferred by the free-immunity of a tubercle infection which has been completely quelled is rather hazy; but its trend suggests a short duration; perhaps, in general, a year or two or so.

The above considerations ascribe the various main outcomes of tubercle infection (no clinical disease; clinical disease with recovery; clinical disease with death) to the numerical interplay of the four above described units, as controlled by a fifth very powerful factor, namely, the *speed* with which the infected tissues react on stimulation by the third unit (the specific immunogenic unit), to produce the fourth unit (the specific active immunity unit), which latter unit, once it appears, has a practically immediate bacteriostatic (probably bactericidal) effect.

[6] The immunity sometimes found in an uninfected child (for example, measles, diphtheria, etc.) does not originate in the child's tissues but in the at-some-time-infected tissues of his mother.

Among North American whites it would appear, as a first approximation, that about 75 per cent possess time-lags short enough *in re* tubercle to ensure (on infection) escape from material damage; contrasting with the remaining, say 25 per cent, some of whom (17 per cent?) possess moderately long time time-lags and, on infection, show clinical disease and recovery, while the rest (8 per cent ?) possess very long time-lags and, on infection, die from their infection.

Chiefly because of their short time-lags, the 75 per cent show, on infection, (see table 4) features contrasting strongly with those shown on infection by the 25 per cent (see table 7).

Thus, the 75 per cent show, relative to the 25 per cent:

(a) *Early appearance of concurrent immunity*—hence
(b) Over-all brevity of their infection-careers, as measured in number of fissions—hence
(c) Short periods of fissions on the full logarithmic scale—hence
(d) Small yields of total bacilli—hence
(e) Small yields of total bacillary quotas—hence
(f) (*1*) Little pathogenic effect; but also (*2*) little total immunity, concurrent or free—hence
(g) (from (f) *1*) (*1*) Little total damage; (from (f) *2*) (*2*) early and rapid accumulation of the small free immunity—hence
(h) (from (g) *2*) Early fading of this small free immunity—hence
(i) Brevity of the free immunity protection against "repeat" infection.
(j) (from (d) and (f) *1*) Low or absent infectiveness of the infectees to other persons—hence
(k) Low or absent infectiveness of the infectees to themselves, that is, few and small, or no reëntering reinfections occur.
(l) All exogenous reinfections, contact or reëntering, in short-time-lag persons, necessarily encounter the same short time-lag as did their original infections; hence are ended by their own early-appearing concurrent immunity in an equally short period. Moreover, they are subject to the early-appearing free immunity of their original infections which may reduce or terminate them even before they would otherwise have ended by themselves. (See table 6.)
(m) After the small free immunity has faded to "reversion" (that is, to nonallergy), a "repeat" infection induces a quite similar, because necessarily also a short time-lag, infection course, which similarly ends in "no clinical disease."

Quite evidently, the 25 per cent, chiefly because of their long time-lags, present the same above features as the 75 per cent, *but exactly in reverse;* with, of course, the exception that the 8 per cent who die show no "free" immunity and hence none of its consequences.

Note from (f) and (g) above that the small total bacillus load of the short time-lag infectee induces correspondingly but little total immunity, concurrent and free; it is only because of its early appearance that this small concurrent immunity can so promptly and effectively quell the infection; providing also a (small) postinfection surplus of free immunity, protective for a time against further infection.

Conversely, the relatively huge total bacillus load of the long time-lag infectee induces a correspondingly huge total immunity, concurrent and (in the 17 per cent who recover) free. But this huge concurrent immunity, because of its late appearance, fails to forestall damage in the 17 per cent; and, appearing still later in the 8 per cent, fails also to forestall death.

Also, in the 75 per cent ("no clinical disease") and in the 17 per cent ("clinical disease and recovery"), the larger the initial dose, the larger will be the free immunity finally attained. (See tables 4, 6, 7.)

It thus would appear that it is not the *initial* size of the initial dose which controls the outcome of infection, but the size of the *total* bacillus load which may be attained by the serial fissions of the initial dose; the size of the *total* bacillus load which may be thus attained being controlled, primarily and chiefly, by the length of the immunity time-lag; since it is this length which determines at what stage of the bacillus-fission-output fission-checking due to immunity will begin; and hence determines the efficiency which the latter can achieve in cutting down the infection. (See Random Factors, later.)

Besides the outstanding effects of

(a) Concurrent immunity in checking fission—and often in ending it—other causes of fission-check are
(b) Loss of living bacilli from the infectee's body in his discharges—losses which are coincident with, and in fact are the causes of, his periods of infectiveness to his associates and to himself (see tables 2 and 5);
(c) Lodgment of bacilli in areas nutritionally unfavorable to fission, for example, original lodgment in, or transfer (metastasis) to, areas of, say, the muscular system rather than in or to lung areas;
(d) Changes in a milieu, at first favorable to fission, such that it becomes unfavorable to fission, for example, the disappearance of bacilli following the collapse of an actively infected lung;
(e) Some forms of chemotherapy—less evident, at present, as to tubercle bacilli than as to some other pathogens;
(f) Metastasis, in which the loss of living bacilli from the local lesion parallels very closely in miniature the losses of (b) above, and may even result in the healing of the local lesion from which the bacilli are extruded; as well as in the setting up of a new lesion in one or more of the new areas in which the extruded bacilli may locate (see tables 2 and 5);
(g) "Latency" of the bacilli—if and when it may occur.
(h) It is not improbable that "spontaneous" failures to fission may be shown by one or two or a few of the members of a fission-crop, all the rest fissioning normally; possibly such failures are due to structural or metabolic defects in the bacilli involved.

For example, in observing microscopically typhoid, diphtheria or other bacilli while most of them are fissioning well (as in "hanging-block" preparations) (3), an occasional bacillus will fail to fission, although in the same milieu, even in the same microscopic field, as actively fissioning confreres. Such losses, however, in the tissues are probably rather negligible.

TABLE 1

Fission Schedules, illustrative of text herewith

Basic data

SCHEDULE *a* (Strict logarithmic series)		SCHEDULE *b* (Schedule *a* accumulated)	SCHEDULE *c* (Initial dose, 1024 times schedule *a*)	
Initial Dose	1x	1x	Initial Dose	1,024x
Fission 1	2	3	Fission 1	2,048x
2	4	7	2	etc.
3	8	15	3	
4	16	31	4	
5	32	63	5	
6	64	127	6	
7	128	255	7	
8	256	511	8	
9	512	1,023	9	↓
10	1,024x	2,047x	10	1,048,576x
11	2,048	4,095	11	etc.
12	4,096	etc.	12	
13	8,192		13	
14	16,384		14	
15	32,768		15	
16	65,536		16	
17	131,072		17	
18	262,144		18	
19	524,288	↓	19	↓
20	1,048,576x	2,097,151x	20	1,073,741,824x
21	2,097,152	etc.		
22	4,194,304			
23	8,388,608			
24	16,777,216			
25	33,554,432			
26	67,108,864			
27	134,217,728			
28	268,435,456			
29	536,870,912	↓		
30	1,073,741,824x	2,147,483,647x		

Schedule *c*:

Total bacilli = 2,147,482,624x
Total quotas = ditto

Compare above *total* bacilli and *total* quotas, sched. *c*, fs. 20, with *total* bacilli and *total* quotas of sched. *a*, fs. 30. The difference re each is the 1,023x of sched. *b*, at fs. 9

Schedule *a*:

Total bacilli = 2,147,483,647x
Total quotas = ditto

Total allergenic units = ditto
Total pathogenic units = ditto
Total immunogenic units = ditto

Schedule *b*: These figures show the *total bacilli* which have appeared (hence also the *total quotas*) by each fission (incl.)

Total immunity units = none *in vitro*; nor *in vivo* during the time lag

Sched. *a*, fs. 10, shows 1,024x as all the living bacilli at this fission. Sched. *b*, fs. 10, shows this 1,024x living bacilli plus their 1,023x predecessors, which latter have disappeared by fissioning; and so likewise for every fission item of sched. *a* and *b*.

Notes to table 1: Table 1, schedule *a*, presents (but to fission 30 only) the sort of theoretical schedule which any fissioning microörganism would present, if every individual cell fissioned perfectly and the fissioning continued indefinitely. "Living" viruses, and even the "huge molecules" of the tobacco-leaf mosaic disease, whether "living" things or not, certainly multiply; and, if they multiply by dividing into two similar bodies, cannot but tend to follow this same schedule—until such time as such division is checked in some way. Therefore, this schedule *a* may be regarded as a theoretical datum line, from which the actual fission-schedules of reality depart, because of various agencies which interfere with fission (see text).

Such causes of fission-check always arise, both *in vitro* and *in vivo*. Hence schedule *a* is never fully realized in nature.

It has been calculated that a single bacillus, fissioning unchecked about as fast as the typhoid bacillus (say every 20 to 30 minutes) would produce descendents enough to fill all the basins of all the oceans of the earth in 3 days—and in 5 days (say 240 to 360 fissions?) could form a bacillus-mass as large as the whole globe. The tubercle bacillus, under like conditions, but fissioning only about once a day, would take perhaps a year to achieve equal results.

Obviously, powerful bacteriostatic and bactericidal agencies continually operate *in vitro* and *in vivo*, obviating such cosmical catastrophes! Of these, doubtless the most wide-spread and influential, *in vitro*, is lack of the required nutritional supplies; *in vivo*, tissue-opposition, i.e., "immunity" in its broadest sense.

For the purposes of tubercle epidemiology, the initial dose, 1x, of schedule *a* indicates the "modal" number of living virulent human type tubercle bacilli which actually become so successfully lodged in the tissues as to grow and fission therein.

The numerical value of this "x" in the natural infections of humans is, of course, always unknown, and doubtless varies from infectee to infectee in correlation with many factors, elsewhere discussed (1, 2). In experimental animals, however, the numerical value of this "x" may be adjusted at will.

The *integers* of schedule *a* indicate the strictly logarithmic fission-increases of the 1x which would necessarily occur, provided the fissions continue wholly unchecked, which they never do.

The nearest widely known approach, *in vivo*, to schedule *a* (*re* tubercle) would appear to be presented by guinea pigs; for guinea pigs, although capable of developing immunity, if given time enough, (for example, in response to vaccines) are so slow in their immunity response that living virulent infections invariably end fatally before the guinea pig's immunity can be adequately mobilized.

A similar approach to schedule *a* is found also in some humans but only in the relatively few (8 per cent?) of the total human North American white infectees who show equivalently long immunity time-lags. The vast majority of persons infected with the tubercle bacillus (92 per cent?) show their fission-schedules (tables 4 to 7) as much modified by a relatively early appearance of immunity.

Nevertheless, table 1, schedule *a*, sets forth certain general structural principles common to all the schedules, however modified; thus, unless and until immunity or other cause of fission-check appears (hence through the period, be it short or long, of the immunity time-lag) all schedules of all tables tend to show strict logarithmic fission increases, that is, each fission yields a fission-crop of bacilli just twice as numerous as the bacilli of the immediately preceding crop which gave rise to it. Moreover, every such fission-crop equals twice the initial dose, 1x, plus twice the sum of *all* the *fission-crops* which preceded it; or, if the initial

dose, 1x, be included, every fission-crop equals the total preceding bacilli plus 1x bacilli (schedule *b*).

These preceding bacilli have, of course, disappeared; not by death or other direct loss, but in the very process of fissioning, that is, in becoming their immediate successors. Before thus disappearing by fissioning, each bacillus has formed, during the one fission-interval which constitutes its brief life, its one quota of bacillary products; each quota containing allergenic, immunogenic and pathogenic elements. The schedule *b* items therefore record both the *total* bacilli which have appeared and, necessarily also, the *total* quotas which they have furnished; one quota from each bacillus.

For example: At fs. 6 of schedule *a*, 64 living bacilli exist; 63 more (initial dose to fs. 5, inclusive) have existed and have disappeared by fission, making 127 bacilli in all (schedule *b*); but the 63 disappeared bacilli have left their 63 quotas, which, added to the 64 quotas contributed by the 64 living bacilli of fs. 6, make up 127 quotas in all (schedule *b*). And so likewise at every fs. of schedules *a* and *c*.

Since each quota contains one immunogenic unit there have appeared for each crop of living bacilli (in schedule *a*) a number of immunogenic units almost twice as large (schedule *b*).

Initial dose: If "x" (in schedule *a* and schedule *c*) = 1 bacillus, the integers of schedule *a* and schedule *c* indicate, at each fission, the actual number of individual living bacilli then existing. Then, table 1, schedule *c*, would indicate that the initial dose is 1,024 individual bacilli, that is, more than 1,000 times the initial dose (1 bacillus) of schedule *a*. In other words, schedule *c* begins with 1,024 bacilli, which is the same number of bacilli as is reached by schedule *a* (if x = 1) at its fs. 10. Thereafter both schedules show the same series of numbers of bacilli in their fission-crops; but schedule *c* evidently shows each number just 10 fissions earlier than schedule *a*.

It is therefore clear that increasing the initial dose thus 1,024 times has hastened the progress of the infection by only 10 fissions; or, at one fission per day, by only ten days; that is, schedule *c* would arrive at a case-precipitating number of bacilli about ten days before schedule *a*.

Such a ten-day difference in the date of the beginning of damage means merely a shortening of the incubation period by ten days—an inconsiderable period in a guinea pig infection; and impossible of recognition at present in a human infection. For in the human the mere establishment that infection has occurred, through a tuberculin test, has a time variation of about four weeks, since the tuberculin reaction may appear in about three weeks after infection or be delayed up to about seven weeks.

If now schedule *c* be taken to have an initial dose of 1,048,576 individual bacilli (equal to schedule *a*, fs. 20, if x = 1), this dose, more than a million times the initial dose of schedule *a*, will hasten schedule *c*, as compared with schedule *a*, by 20 fissions—say by twenty days—or still somewhat less than the variation in the first appearance of the tuberculin reaction in the human being.

The above considerations relate only to the figures of living bacilli at the fissions. If the bacilli preceding the fissions also be considered (and their corresponding quotas), schedule *c* at its fs. 10 (if x = 1) shows the same number

of living bacilli, 1,048,576 as schedule *a* at its fs. 20, but a lesser number of total bacilli and of total quotas. For schedule *c* shows, initial dose to fs. 10 inclusive, 2,096,128 total bacilli, hence the same for total quotas; while schedule *a*, initial dose to fs. 20 inclusive, shows 1,023 more of each.

Hence, although the larger initial dose reaches damaging numbers of living bacilli the more rapidly, yet its total damaging equipment (that is, its total bacilli, hence its total quotas) is less than that of the smaller dose, when the small dose later arrives at a fission-crop showing the same number of living bacilli. The greater the difference in size between the larger and the smaller dose, the greater relatively will be the handicap of the larger initial dose in this respect.

TABLE 2

Extrusion

Illustrative of fission-check by extrusion of bacilli from a fission-crop of an infection, in the *absence* of immunity. Such extrusions occur in guinea pigs; in the 8 per cent (?) of humans who show comparably long time-lags, and may occur in any human infectee during his time-lag, be it short or long.

SCHEDULE *a* (Strict logarithmic fission; no extrusion)		SCHEDULE *b* (Schedule *a*, modified by extrusion of 5x bac. at fs. 10)	SCHEDULE *a* MINUS SCHEDULE *b*, FISSION BY FISSION
Initial Dose	1x	1x	0x
Fs. 1	2	etc.	0x
2	4		0
3	8		0
4	16		0
5	32		0
6	64		0
7	128		0
8	256	(1,023x Tot. bac. I. D. to Fs. 9, incl.)	0
9	512		0
10	1,024	1,024x − 5x = 1,019x; × 2 = Fs. 11	0
11	2,048	2,038 − 0 = 2,038x; × 2 = Fs. 12	10x
12	4,096	4,076 − 0 = 4,076x; × 2 = Fs. 13	20
13	8,192	8,152 − 0 = 8,152x; × 2 = Fs. 14	40
14	16,384x	16,304x	80
Total bacilli	32,767x	32,617x; Sched. *a* minus Sched. *b* = Tot. bac. 150x	

"Extrusion" is used to indicate the departure of living bacilli, by lymph or blood-stream or rupture of a surface lesion, from a focus in which fission is proceeding; thus reducing the bacilli left behind to continue fission in the focus from which these living bacilli are extruded.

This reduction of the bacilli in the original focus occurs whether the extruded bacilli become lodged in a new area of the body tissues or pass entirely out of the body-tissues by way of the body-discharges. If the former occurs the extruded bacilli may find the new area unfavorable and perish; or favorable, that is, permitting the extruded bacilli to continue fission, thus setting up a new focus. If, however, the living extruded bacilli pass out of the body in the body discharges (thus benefiting the infectee), they render the latter infective;

thus providing the outstanding class-feature of all infections, namely, their transmissibility to other living bodies.

Without extrusion, the fissions of the original infection can extend its focus only locally. By extrusion of some living bacilli, whether free or contained in cells which depart with them, the transmission of the local infection to new areas of the *same* body may be achieved (metastasis). The transmission of the disease to *new* bodies, (contact infection), may occur at the same occasion or separately. Also, through the inhalation, ingestion, etc., of his own discharges thus infected by the infectee who discharges them, a "reëntering" infection may occur in the infectee's own body—a round-about variety of metastasis, in essence. Moreover, a single extrusion may distribute some of its bacilli to each of the various "fates" which may befall such extruded bacilli.

By inspection of table 2, it will be seen that the extrusion of only 5x bacilli (at fs. 10) has reduced the existing bacilli (at fs. 14) by 80x bacilli; which is 16 times the actual number, 5x extruded. Also, the total bacilli to and including fs. 14 have been reduced by 150x bacilli; which is 30 times the 5x bacilli extruded. This arises because any loss of bacilli at any fission, whether by extrusion or otherwise, involves also the loss of those fission-descendants which the lost bacilli would have produced *in situ*, had they not been lost. Hence, if schedule *a* and schedule *b* are continued to fs. 20, schedule *a*, fs. 20, minus schedule *b*, fs. 20 = 5,120x living bacilli; while the total bacilli of schedule *a*, minus the total bacilli of schedule *b* = 10,230x bacilli—all due wholly to the one extrusion of 5x bacilli at fs. 10.

True, the 5x bacilli extruded at fs. 10 are but about 0.5 per cent of the 1,024x bacilli of schedule *a*, fs. 10, and this percentage remains constant throughout all subsequent fissions, however many.

But the earlier a given loss occurs, the more effective it is; for a 5x loss at fs. 9 would be about 1 per cent of the 512x bacilli of schedule *a*, fs. 9; at fs. 8, the similar loss would be about 2 per cent; at fs. 3, about 62 per cent; while a loss of 4x bacilli at fs. 2 would of course end all fissioning at the local infection.

On the other hand, the later a given extrusion occurs, the less its percentage effect; for example, a 5x loss at fs. 14 is but 0.03 per cent of schedule *a*, fs. 14.

In nature, extrusions of living tubercle bacilli from the tissues into the discharges, once they begin, are likely to be more or less continuous, to fluctuate and to reach, if and as the infection grows much, numbers in the many millions per day. Nevertheless, in the guinea pig and in the 8 per cent (?) of human infectees who have comparably long immunity time-lags, it is evident that even such great extrusion losses are not great enough to make up for the lack of immunity.

At the other extreme, the human short time-lag infectee shows small losses of this nature; but his early acting, hence highly efficient, immunity response requires no reinforcement by extrusion.

There remains the human infectee whose time-lag is intermediate and his margin of safety rather small or doubtful. Here extensive losses of living bacilli from the tissues may tip the scales favorably to him. (See table 7.)

If the extruded bacilli, instead of escaping from the tissues in the body discharges, should remain in the tissues and set up one or more successful metastatic foci, they would not add to the previous total bacillus load of the tissues but would merely transfer their activities from the focus of the original infection to a new focus or foci; depleting the old focus, but reproducing in the new exactly the same number of bacilli as they would have reproduced in the old focus, had they remained there. (See table 3.)

TABLE 3

Exogenous and endogenous reinfection in absence of immunity

Illustrative of the numerical effects of various exogenous reinfection doses

SCHEDULE *a* (Original infection. Strict logarithmic fissions. No immunity)		SCHEDULES *b* TO *k* EXOGENOUS REINFECTIONS (Strict logarithmic fissions; no immunity)										*l* TOTAL REINFECTION ONLY	*m* TOTAL COMBINED LIVING BACILLUS LOAD AT EACH *a* FISSION
	a	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*i*	*j*	*k*	(*b* to *k*)	(*a* + *b* to *k*)
Initial Dose	1x	·										0x	1x bacillus
Fs. 1	2	1x										1	3
2	4	2	1x									3	7
3	8	4	2	1x								7	15
4	16	8	4	2	1x							15	31
5	32	16	8	4	2	1x						31	63
6	64	32	16	8	4	2	1x					63	127
7	128x	64	32	16	8	4	2	1x				127	255
8	256	128	64	32	16	8	4	2	1x	0		255	511
9	512	256	128	64	32	16	8	4	2	1x		511	1023
10	1,024x	512	256	128	64	32	16	8	4	2	1x	1,023x	2,047x bacilli
11	2,048x												
Fs. 17	131,072											131,071x	262,143x
18	262,144											262,143	524,287
19	524,288											524,287	1,048,575
20	1,048,576											etc.	etc.
	etc.												

Contrast these results, immunity *absent*, with those of table 4, in which concurrent immunity appears at fs. 3.

Notes to table 3: "Exogenous reinfection" (superinfection), in current usage, indicates the occurrence of an exogenous infection during the course of a preceding infection. (An exogenous infection following the termination of all preceding infections is herein distinguished as a "repeat" infection.)

Current usage recognizes two forms of reinfection, exogenous and endogenous. The former indicates an addition to the bacilli already in the tissues of wholly new bacilli from extraneous sources. Endogenous reinfection, in strong contrast, indicates merely that further developments have occurred among the bacilli already in the tissues, without any reinforcement of new bacilli from outside sources. In this sense, every fission of the bacilli already existing in the tissues is, in essence, an endogenous reinfection—adding further bacilli to the total bacillus load of the tissues, but wholly from within.

Endogenous reinfection is therefore a "normal" biological consequence of the inherent interactions of any infection with the tissues in which it is lodged; but exogenous reinfection is due to the "sociological accident" of exposure to an outside source of infection,

from which is received an increment of new bacilli which, small or large, is evidently above and beyond any increments possible to the already existing infection from its own activities alone.

Table 3 illustrates exogenous reinfections such as may occur (*1*) in guinea pigs—through artificial inoculations, or through exposure to infective contacts; (*2*) in that 8 per cent (?) of all human infectees who have similar very long immunity time-lags; (*3*) in the remaining 92 per cent (?) of all human infectees; but, of course, only during the existence of their relatively short immunity time-lags.

Schedule *a* represents the early course of an original infection, initial dose 1x bacilli. Schedule *b* represents the early course of an identical exogenous reinfection dose, entering the tissues at the time of *a*, fs. 1. Schedules *c* to *k* are identical reinfections, one of which enters at each subsequent fission of *a*.[7]

The outstanding features of table 3 appear thus: (*1*) The *combined* total bacillus load (original infection *a* + reinfections *b* to *k*) is shown, schedule *m*, for each fission of *a*. Note that each fission item of *m* is necessarily just 1x bacillus *less* than the *next* fission item of *a*; and that this relation necessarily maintains itself, however far table 3 is carried out; that is, however long a daily reïnfection of 1x be added to the original infection *a*.[8] (*2*) The later, in the course of the original infection *a*, the reinfection series begins, the less will be its effect in raising the combined load. Thus, if *c* were the first reinfection of the series, table 3, *b* being omitted, *a* fs. 10 + reinfections *c* to *k* = 1,535x instead of the 2,047x of schedule *m*. (*3*) Although daily *exposure* to infection and reinfection is commonplace, daily *implantation* in the exposee's tissues of the bacilli thus inhaled or ingested or both is rare. Hence, in the ten days covered by the 10 fissions of schedule *a*, table 3, the occurrence of more than one reinfection seems highly improbable. (Nonreacting entrants to medical or nursing courses, sanatorium service, etc., usually show 20 to 30 per cent of their number still nonreactors after a whole year's exposure. Can *exogenous reinfections* occur more readily than *original infections*?)

Simple inspection of table 3 shows that no one, or even any three, of the rein-

[7] Note that, in natural contact tubercle infections, the occurrence of such a continuous series of exogenous reinfections, so early in the course of the original infection, must be extremely rare; although much later such a series of daily reinfections from the infectee's own infective discharges (reëntering reinfections) apparently is common, and in size may be high multiples of *a*'s initial dose, 1x. But by that time, *a* will itself have reached, by its own fissions, such huge figures that even very large reinfection doses will add but a small per cent of increment to them.

[8] F (R + 1) − Rx is a formula which yields the *combined* load (schedule *m*). Let F = any given fission of *a*; let R be the *integer only* of the initial doses of the series of reinfections, *b* to *k*. For example, in table 3, R = 1; hence, since *a*, fission 6 = 64x, the formula yields 64x (1 + 1) − 1x = 128x − 1x = 127x (see schedule *m*), that is, 1x *less* than *a* fission 7; therefore, the *combined* infection figure is reached by *a alone*, less than one day later. Also, if R = 10, the formula again applied at *a* fission 6, yields 64x (10 + 1) − 10x = 694x; that is, less than *a* fission 10; at which latter *a alone* will arrive less than 4 fissions later (= less than four days later). Also if R = 1,000 (a quite incredible series figure at early stages of an infection), the formula yields for *a* fission 6, 64x (1,000 + 1) − 1,000x = 63,064x; that is, *less* than *a alone*, fission 16; which later (65,536x) *a alone* would reach ten days later.

fections, alone or together, can yield at any fission of *a* more than seven-sixteenths of the next fission of *a alone*. Also, a single reinfection of 1,000x at *b* will yield 512,000x bacilli at the time of *a* fs. 10; the *combined* infection being then 513,024x; which figure *a alone* will exceed at its fs. 19 (524,288x) nine days later.

Contrast the same single reinfection of 1,000x, if delayed to *k*. The combined infection at the time of *a* fs. 10 becomes 2,024x, or 24x less than *a alone* at its fs. 11.

So far then as the *total bacillus load* of the tissues is concerned, a daily series of exogenous reinfections, each equal to the initial dose of the original *a*, is less than equivalent to doubling the initial dose of the original infection alone; which doubling would hasten the infection by one fission-interval (in tubercle by perhaps one day—in typhoid by perhaps twenty to thirty minutes).

So also if the initial doses of the reinfections *b* to *k* be 1,000x each, this is less than equivalent to making the initial dose of *a* alone 1,001x.

But the exogenous reinfections *b* to *k* have another effect, apart from increasing the total bacillus load of the tissues as above described; namely, the setting up of *new foci* of infection in the tissues. For the reinfections *b* to *k* are not likely to locate at the exact site of *a*; nor is it likely that a new reinfection will locate at the exact site of a previous reinfection.

Hence it is rather probable that the 1,023x exogenously derived reinfection bacilli of schedule *l* have set up not less than 10 *new* foci in addition to that one focus occupied by *a*. These 11 foci (at the time of fs. 10 of *a*) may therefore be visualized as containing bacilli ranging in number from the 1,024x of *a* to the 1x of *k*; total bacillus load, the 2,047x of *m*.[9]

ENDOGENOUS REINFECTIONS

This setting up of 10 new foci through exogenous reinfection as above described may also be accomplished in another way, and in the total absence of any exogenous reinfection whatever; that is, by metastasis from *a*.[10]

Such metastatic (hence endogenous) reinfections from the original infection may be identical in size and number with those from the exogenous reinfections of table 3; but such exogenous reinfections differ basically from the metastatic (that is, endogenous) reinfections in several respects.

(*1*) Obviously in origin—for the exogenous reinfections require contact with a source of reinfection external to the infectee's tissues; the endogenous metastases, deriving wholly from biological changes (bacterial and tissue changes), are necessarily wholly from internal sources, that is, from already existing infections.

[9] The question arises—do the 1,024x bacilli of *a*, fission 10, concentrated in one focus, mean more (or less?) ultimate damage to the infectee than the almost equal number of reinfection bacilli (1,023x) distributed in 10 different foci? Doubtless the answer must depend in part on the particular sites of the various foci; but a complete answer does not yet appear.

[10] It is perhaps unlikely that numerous metastases should occur so early as *a* fission 1 to fission 10. But these schedules are illustrative only of the principles which the speed of reaction hypothesis postulates as governing the huge figures which later appear—figures too huge and unwieldy to be readily presented or readily grasped.

(2) The exogenous reinfections add to the total bacillus load already existing in the tissues; but the endogenous reinfections are achieved by mere rearrangements of, not by additions to, that already existing bacillus load; which total bacillus load therefore increases only by its own fissions, *not* by additions from outside.

(3) The exogenous reinfections leave the original infection, *a*, table 3, untouched; but the endogenous reinfections consist of transfers from the original infection, and therefore correspondingly deplete it or may even wipe it out. Thus: Suppose schedule *a*, fs. 1, to extrude 1x bacilli, which then set up schedule *b*; the latter will show at the time of fs. 10 of *a*, 512x bacilli. This is exactly the same 512x bacilli which the 1x extruded bacilli would have yielded in *a* at its fs. 10 if the 1x bacilli had remained in *a*; and so for each 1x transferred from *a* to set up *c* to *k*. Schedule *a* loses these 1x extrusions from its own focus, but each such loss yields in its new site (*b*, *c*, etc.) exactly the number of bacilli which it would have yielded had the 1x bacilli remained in their old site, *a*. Therefore, it is evident that this depletion of *a* by metastases to *b*, *c*, etc. neither adds to nor decreases the total bacillus load of the tissues. For, without metastases, the total living bacillus load at *a* fs. 10 is 1,024x. With the metastases, *b* to *k* yield 1,023x bacilli at the time of *a* fs. 10; *a* fs. 10 itself yielding then but 1x; hence the total bacillus load is still 1,024x.

This reduction of *a* fs. 10 from 1,024x to 1x results thus. Since *a* fs. 1 = 2x and is taken to extrude from it the 1x which sets up metastasis *b*, 1x alone remains to fission in *a* — yielding *a* fs. 2 = 2x; this 2x also extrudes 1x, which sets up metastasis *c*, leaving 1x alone to fission in *a* — yielding *a* fs. 3 = 2x. Evidently since this loss of 1x continues at each fission of *a*, 1x alone remains to fission in *a* at its fs. 10.

Should *a*, at any fs., metastasize the whole of its fission-crop at that fs., *a*, obviously, would be ended.

But the thus metastasized bacilli would in effect carry on *a*, in their new site (or sites); any lesion at the former site of *a*, then undergoing repair but the metastasized bacilli setting up a new focus (or foci) at *b*, *c*, *d*, etc.

Thus *a*, in essence, continues; but in one or more new foci, *not* in its original focus.

The foregoing considerations certainly appear to justify the conclusion that endogenous reinfection by itself, in the absence of immunity, develops through fission and metastasis, quantities of bacilli, distributed in numerous foci, and does so, regardless of whether or not exogenous reinfection occurs also. If exogenous reinfection occurs also, it merely hastens somewhat the progress of the total infection.

Hence both exogenous reinfection and metastasis tend to increase the number of foci of infection. But the exogenous reinfection also increases the total bacillus load of the tissues, which metastasis does not.

On the other hand, under current sociological conditions, exogenous reinfection, "a sociological accident," tends to be, relative to metastasis, rather infrequent, and, in any event, small in size, relative to the total bacillus load; while metastases tend to be frequent and, relative to exogenous reinfections, of large size.

Obviously metastases may arise from the reinfection foci themselves (*b* to *k*, table 3) as well as from the original infection *a*, whether these reinfections be set up from exogenous sources or from original infections, such as *a*, or from reinfections, such as *b* to *k*, that is, from endogenous sources. Hence, in either or both ways, great increases in bacilli and in foci (hence ultimately in lesions) continue to occur; and, in the absence of immunity, this rising flood of bacilli and lesions ultimately but inevitably overwhelms the infectee; for, in the absence of immunity, or other adequate means of fission-check (chemotherapy, etc.), there is nothing adequate to stop the flood.

For example: The normal guinea pig has so long an immunity time-lag that, on inoculation with a single dose of living virulent human type tubercle bacilli, he develops fatal damage before material immunity can appear.

The vast numbers of guinea pigs inoculated for diagnostic purposes receive such a single dose and are thereafter meticulously guarded against any form of further exogenous infection whatever; except, of course, from his own discharges. The latter (reëntering reinfections) constitute, as elsewhere already pointed out, a round-about form of metastasis from his own bacilli, and in that sense are practically equivalent to endogenous reinfections. Yet, such guinea pigs invariably perish—thus demonstrating that, in guinea pigs, exogenous reinfection from extraneous sources is quite nonessential to the occurrence of damage sufficient to ensure death.

The numerical rôles of exogenous reinfections and of endogenous reinfections (metastases), in the presence of immunity, are illustrated in the remaining tables 4 to 7. These tables are based on the same principles as are tables 1 to 3, but yield very strongly contrasting pictures—namely, all the contrast between 100 per cent death in the guinea pig infectees (which show no material immunity) and 92 per cent (?) escape from death in the human infectees (who show material immunity).

TABLE 4

Illustrative of modifications of strict logarithmic fissioning by concurrent immunity; dealing with very short immunity time-lags such as are taken to occur in that 75 per cent of human infectees who show no (or no material) damage

SCHEDULE *a* (Concurrent immunity appears at Fs. 1. Time-lag = 1 fission-interval)

	Col. A Bacilli appearing		Col. B Concurrent immunity		Col. C Bacilli left to fission
Initial Dose	1x	−	0x	=	1x
Fs. 1	2x	−	1x	=	1x
2	(2x)	−	2x	=	0x
Total	5x	−	3x	=	2x

Fs. 2 leaves 2x free imm. = total C

SCHEDULE *b* (Concurrent immunity appears at Fs. 2. Time-lag = 2 fission intervals)

	Col. A		Col. B		Col. C
Initial Dose	1x	−	0x	=	1x
Fs. 1	2x	−	0x	=	2x
2	4x	−	1x	=	3x
3	6x	−	2x	=	4x
4	8x	−	4x	=	4x
5	(8x)	−	6x	=	2x
6	(4x)	−	4x*	=	0x(4x)
Totals	33x	−	17x	=	16x

* leaving 4x free imm. (8 − 4)

Fs. 5 and 6 leave 12x further free imm.

Total 16x free imm. units = total C

SCHEDULE *c* (Concurrent immunity appears at Fs. 3. Time-lag = 3 fission intervals)

	Col. A		Col. B		Col. C
Initial Dose	1x	−	0x	=	1x
Fs. 1	2x	−	0x	=	2x
2	4x	−	0x	=	4x
3	8x	−	1x	=	7x
4	14x	−	2x	=	12x
5	24x	−	4x	=	20x
6	40x	−	8x	=	32x
7	64x	−	14x	=	50x
8	100x	−	24x	=	76x
9	152x	−	40x	=	112x
10	224x	−	64x	=	160x
11	320x	−	100x	=	220x
12	440x	−	152x	=	228x
13	576x	−	224x	=	352x
14	704x	−	320x	=	384x
15	(768x)	−	440x	=	328x
16	(656x)	−	576x	=	80x
17	(160x)	−	160x*	=	0(544x)
Totals	4,257x	−	2,129x	=	2,128x

* Leaving 544x free imm. (704 − 160)
Fs. 15, 16, 17 leave 1,584x free imm.
Total 2,128x free imm. = total C

at each fission:
- Col. A = total living bacilli then existing
- Col. B = total concurrent immunity units then available
- Col. C = A − B = total living bacilli left to fission

Figures in parentheses indicate free immunity units: the total of which = total C

(Further details in text below)

These three schedules are identical in pattern, differing only in the lengths of their respective immunity time-lags by one fission interval, as indicated by the initial zeros of the respective B columns. Schedule *c* only will be discussed in detail, but the same principles of structure may be traced in schedule *a* and schedule *b*.

Keep always in mind that each item of each column A represents all the living bacilli that exist at the time of that item; because the preceding items of column A represent bacilli that have disappeared, while the succeeding items have, of course, not yet appeared.

Each schedule, on its termination by the disappearance of all living bacilli, thus ending the fission-career of the infection, presents in retrospect the summed-up history indicated by the respective totals of its various columns—thus

	IMMUNITY TIME-LAG IN FISSION INTERVALS	INITIAL DOSE	TOTAL FIS-SIONS	TOTAL BACILLI APPEARED BY FISSION	TOTAL BACILLI IN ALL	TOTAL IMMU-NITY		USED OR CONCUR-RENT IMMUN-ITY		UNUSED OR FREE IMMU-NITY
Schedule *a*	1	1x	2	4x	5x	5x	=	3x	+	2x
b	2	1x	6	32x	33x	33x	=	17x	+	16x
c	3	1x	17	4,256x	4,257x	4,257x	=	2,129x	+	2,128x

Thus these three infections, each beginning with the same size of initial dose, 1x, require for complete wiping out by immunity, respectively, 3x, 17x, and 2,129x immunity units; the great difference in these concurrent immunity requirements depending solely on how soon, in the fission-careers, the concurrent immunity begins to act; schedule *c* requiring about 700 times as much concurrent immunity as schedule *a*, about 125 times as much as schedule *b*.

Schedule c: The length of the time-lag is 3 fission-intervals; hence the 1x immunity units elicited from the tissues by the 1x immunogenic units produced by the 1x bacilli of the initial dose, column A, are postulated to appear after the 8x bacilli of fs. 3 have appeared and have formed their 8x quotas (each quota containing allergenic, pathogenic and immunogenic elements). This 1x immunity is recorded at fs. 3, column B. Similarly the 2x immunity units similarly induced by the 2x bacilli of fs. 1 are recorded at fs. 4, column B and so on. Similarly the 704 immunity units of the 704x bacilli of fs. 14 appear at fs. 17; but are recorded as 160x used immunity units in column B, with the remaining 544x immunity units left over as "free immunity;" in the table, free immunity figures are enclosed in parentheses, to distinguish them from the concurrent immunity units.

Since the 1x immunity units at fs. 3, B, are postulated to quell 1x bacilli of the 8x bacilli fs. 3, A, the 7x bacilli thus left to fission are recorded at fs. 3, C. These 7x bacilli, on fission, become 14x bacilli constituting the fission-crop of fs. 4, A. Similarly this 14x, after producing its quotas, is reduced by the 2x immunity, fs. 4, B, to the 12x bacilli of fs. 4, C, which, on fission, becomes the 24x bacilli of fs. 5, A, and so on; fs. 17 A, 160x bacilli, being wholly quelled by the 704x immunity units induced by the 704x bacilli of fs. 14, A, no bacilli are left to fission, as is shown at fs. 17, C, with (544x) free immunity units over.

Up to and including fs. 16, the column B item at each fs. necessarily is smaller than the corresponding column A item; but at fs. 17, the B item is the larger, thus ending the infection; with 544x (704x − 160x) immunity units over which, having no bacilli left to act on, remain "free" in the tissues.

Evidently the unused immunity units still due to appear from fs. 15, 768x; fs. 16, 656x; and fs. 17, 160x; will also encounter no bacilli until a new exogenous infection is encountered; and as they respectively appear at "constructive" fs. 18, 19 and 20, will add themselves cumulatively to the 544x immunity units already freed at fs. 17; thus making the total free immunity available *at* fs. 17, 544x; *at* "constructive" fs. 18, 1,312x; *at* "constructive" fs. 19, 1,968x; *at* "constructive" fs. 20, 2,128x; the latter therefore constituting the total free immunity of the schedule.

Thereafter, until they gradually "fade," these 2,128x free immunity units obviously are protective against not-too-great further tubercle infections; herein designated as "repeat" infections, since they occur *after*, not *during*, a previous infection.

Hence arises an obvious question—what becomes of the 2,128x allergenic and of the 2,128 pathogenic elements also derived from the 2,128x bacilli of fs. 14, 15, 16 and 17, column A?

At least two alternative answers may be suggested for further consideration. One of these alternatives suggests that the 2,128x free immunity units may each contain both

antibacterial agents (that is, fission-checking agents), and also "antitoxic" agents (that is, neutralizing agents against pathogenic elements).

If so, the 2,128x "antitoxic" agents of the 2,128x free immunity units may neutralize the 2,128x pathogenic elements which accompany them, leaving only the 2,128x antibacterial agents to quell any further bacilli introduced by further exogenous infection ("repeat infection").

Following such neutralization, the immunity of a recovered tubercle case would be antibacterial only, not antitoxic.

The other of these alternatives suggests that tubercle immunity is inherently antibacterial only; that is, possesses no neutralizing power whatever against the pathogenic or allergenic elements of the bacterial quotas. Then the 2,128x pathogenic and the 2,128x allergenic elements would continue to act on the tissues after the living infection has been wholly quelled by the 2,129x units of the concurrent immunity as earlier shown; and would so act until so used up in spite of the 2,128x purely antibacterial units, which, of course, would have no means of stopping them; thus continuing the disease for a time after the living infection has ended.

Since the allergenic elements of the quotas may maintain allergy for some time after the living infection has apparently ended, it does not seem unlikely that the pathogenic elements may similarly continue to act.

On the hypothesis more or less currently accepted that the allergenic element of the bacterial quotas is a powerful, even the predominating, factor in the pathogenic element of the quota, the second alternative presented here seems to be the more likely. Both however lead to the same deduction—that the tubercle immunity of a recovered tubercle case is predominantly, perhaps wholly, antibacterial.

It is of incidental interest to reflect that if either of the above alternatives be applicable to the immunity of a recovered measles case, it would explain very plausibly why convalescent measles serum is of high value for preventing measles only if administered to a measles infectee very soon after his initial infection; that is, while the fission-crops of his measles-virus infection are still relatively small, but fails to prevent the measles attack if administered later in the incubation period, when the virus fission-crops have become so large that the convalescent serum can at most cut their numbers down somewhat but cannot prevent their development entirely.

(The defense of the above suggestion concerning the action of measles convalescent serum and of analogous procedures is too lengthy for further consideration here.)

Similar questions arise regarding the quotas produced by those bacilli that are quelled by the antibacterial element of the concurrent immunity unit; that is, are their allergenic and pathogenic elements or both also quelled by "antitoxic" elements of the concurrent immunity? The solution of the like question already asked regarding the free immunity unit should solve this one also.

Table 5A necessarily shows the same immunity time-lag for the metastasis as for the original infection; for both these infections necessarily occur in the same infectee.

The striking features which table 5A presents are:

(*1*) The extrusion of 5x bacilli from the original infection, if all the bacilli successfully lodge in the tissues and go on fissioning, has apparently no effect on the total bacillus load of the tissues, on the total concurrent immunity used or on the total free immunity finally released.

(*2*) The metastases, in short time-lag infectees, if running independently of the original infection, will end of themselves after the same number of fissions shown by the original infection; but, when affected by the free immunity of the

TABLE 5A

Extrusion

Illustrative of a single extrusion of bacilli from a fission-crop of an infection after concurrent immunity has appeared; that is after the initial period of the time-lag has ended; hence contrasts with table 2, which see. The original schedule from which the extrusion occurs is schedule *c* of table 4.

SCHEDULE *a*

(This is Schedule *c* of table 4; modified by extrusion of 5x bacilli at Fs. 10)

Original infection, modified

		A		B		C	
Initial Dose		1	—	0	=	1	
Fs.	1	2	—	0	=	2	
	2	4	—	0	=	4	
	3	8	—	1	=	7	
	4	14	—	2	=	12	
	5	24	—	4	=	20	
	6	40	—	8	=	32	
	7	64	—	14	=	50	
	8	100	—	24	=	76	
	9	152	—	40	=	112	
Extrusion	10	219	—	64	=	155	5x from 224x
	11	310	—	100	=	210	
	12	420	—	152	=	268	
	13	536	—	219	=	317	
	14	(634)	—	310	=	324	
	15	(648)	—	420	=	228	
	16	(456)	—	456	=	0: (80)	Free Immunity units
							Free Immunity units (from
Total		3,632	—	1,814	=	1,818: (90)	Fs. 14)

Free immunity of Schedule *a*

80x over from Fs. 16; available to Fs. 6, *b*; all 80x used at Fs. 6, *b*
634x from Fs. 14 ; available to Fs. 7, *b*; only 90x used at Fs. 7, *b*
648x from Fs. 15 ; not used at all
456x from Fs. 16 ; not used at all

Total 1,818x immunity units; of which 170x in all are used to help terminate the metastasis, Schedule *b*; leaving to Schedule *a* 1,648x free immunity units

SCHEDULE *b*

(This schedule shows the course of a successful metastasis of the 5 bacilli extruded from Schedule *a*, Fs. 10)

Note: Had the 5x extruded bacilli passed out of the tissues into the infectees's discharges, Sched. *a* would have ended as shown, with 1,818x free immunity units.

But if the 5x extruded bacilli locate successfully in the tissues, they will set up a metastatic (that is, an endogenous) reinfection, as shown below. To this metastasis Sched. *a* then loses 170x of its 1,818x free immunity units.

Metastasis

	A		B		C
Initial Dose	5x	—	0	=	5x
Fs. 1	10	—	0	=	10
2	20	—	0	=	20
3	40	—	5	=	60
4	70	—	10	=	60
5	(120)	—	20	=	100
6	(200)	—	40	=	80
			(80)		
7	(160)x	—	70	=	0x
			(90)		
Total	625x	—	315x	=	310x

Free immunity of Schedule *b*

120x from Fs. 5; av. Fs. 8, *b*
200x from Fs. 6; av. Fs. 9 *b*
160x from Fs. 7; av. Fs. 10 *b*

Total 480x free immunity units. Both *a* and *b* are ended. Grand total free immunity units amount to 2,128x free immunity units.

The original infection, unmodified by extrusion shows

(See table 4, *c*) —	A, 4,257x:	B, 2,129x:	C, 2,128x
table 5, *a* yields	3,632x:	1,814x:	1,818x
Difference	625x	315x	310x

*

which difference is exactly the yield of the metastasis *b*; because the metastasis is arrested at its Fs. 7 by (80 + 90) x free immunity units released by the original infection. Without this, the 5x metastasis would run 10 more fissions, yielding in all 4,257x × 5 bacilli (21,285x bacilli); and 2,128x × 5 free immunity units (10,640x free immunity units).

* This tabulation shows the respective free immunity units of Schedule *a* and Schedule *b*, before adjustment is made for the transfer of 170x free immunity units from Schedule *a* to Schedule *b*. On such adjustment, the final actual free immunity figures become:

For Schedule *a*, (1,818 − 170) = 1,648x) final active
For Schedule *b*, (310 + 170) = 480x) free immunity units
Hence *a* + *b* 2,128 ± 0 = 2,128x

TABLE 5B

Illustrative of a series of extrusions of bacilli from Schedule *a* of table 5A

SCHEDULE *c* (Being Schedule *a* of table 5A further modified by two additional extrusions of 5x at, respectively, Fs. 11 and Fs. 12; that is, three extrusions of 5x bacilli in all; Fs. 10, 11, 12)					SCHEDULE *d* (The metastasis from Fs. 10 of *c*)				SCHEDULE *e* (The metastasis from Fs. 11 of *c*)				SCHEDULE *f* (The metastasis from Fs. 12 of *c*)			
		A	B	C												
Initial Dose		1x —	0 =	1x												
Fs.	1	2 —	0 =	2												
	2	4 —	0 =	4												
	3	8 —	1 =	7												
	4	14 —	2 =	12												
	5	24 —	4 =	20												
	6	40 —	8 =	32												
	7	64 —	14 =	50												
	8	100 —	24 =	76												
	9	152 —	40 =	112												
Extrusion	10	219 —	64 =	155	Initial Dose	5 —	0 =	5								
Extrusion	11	305 —	100 =	205	Fs. 1	10 —	0 =	10	Initial Dose	5 —	0 =	5				
Extrusion	12	405 —	152 =	253	2	20 —	0 =	20	Fs. 1	10 —	0 =	10	Initial Dose	5 —	0 =	5x
	13	506 —	219 =	287	3	40 —	5 =	35	2	20 —	0 =	20	Fs. 1	10 —	0 =	10
	14	(574) —	305 =	269	4	(70) —	10 =	60	3	40 —	5 =	35	2	20 —	0 =	20
	15	(538) —	405 =	133	5	(120) —	20 =	100	4	(70) —	10 =	60	3	(40) —	5 =	35
	16	(266) —	266 =	0(240x)	→ 6	(200) —	40 =	0(80) →	5	(120) —	20 =	20	4	(70) —	10 =	60
							(160)				(80)				20	
									6	(40) —	40 =	0	5	(120) —	(100) =	0
		3,222 —	1,604 =	1,618x		465 —	235 =	230x		305 —	155 =	150x		265 —	135 =	130x

original infection, terminate with fewer fissions and with but a fraction of the bacilli, quotas, etc. which they would otherwise produce.

(*3*) Although table 5A gives but one illustration (5x bacilli extruded at fs. 10 of the original), other similar schedules, similarly constructed, show that precisely similar ultimate figures appear, regardless of the size of the extrusion and regardless also of the particular fission-crop of the original infection from which the bacilli are extruded. For example, extrusion of 2x, or 5x, or 11x, etc. bacilli from any fission-crop of schedule *c* large enough to furnish them will all yield just enough bacilli etc. to make up, in conjunction with the original infection 4,257x bacilli appearing, and the corresponding quotas, immunities, etc. as shown in table 4.

(*4*) In table 5A, the extrusion of the 5x is taken to occur from the 224x of fs. 10, *a*, before the extruded bacilli, which therefore appear in the metastatic focus, have produced their immunogenic units. If, however, the extrusion occurs after the extruded bacilli have parted with their immunogenic units, the ultimate outcome is nevertheless unchanged; that is, the sum of the total bacilli of the original infection and of the metastases, when all are ended, is still *4,257x bacilli.* So also, if the extrusions be multiple (see later).

(*5*) Evidently, then, such metastases can be set up only at the expense of the original infection; they add in no way to the total bacillus load, as exogenous reinfections do, but merely rearrange the distribution of the living bacilli already present. Thus, the extrusion of 5x bacilli from schedule *a* reduces its ultimate total bacillus load from the prospective 4257x bacilli, due at fs. 17 in the absence

of extrusion, to the 3,632x total bacilli shown above at its new terminal, fs. 16. This is a reduction by 625x bacilli, that is, by roughly 14 per cent; which is exactly the 625x "total bacilli appearing" which the metastasis furnishes. Likewise, schedule *a* shows less concurrent and less free immunity than does the original infection without extrusion; but the metastasis schedule *b* exactly repairs these losses also.

(*6*) Thus it becomes possible that the course of the original infection might be abruptly ended by the complete extrusion of the whole fission-crop at any given fission. If a successful metastasis of the whole 224x bacilli at fs. 10 *a* were thus set up, it would be subject to the immunity set free by the bacilli of fs. 7, 8 and 9 of schedule *a*, and in this order. Hence the 224x metastasis would proceed to follow in its new site exactly the same fission-schedule which it would have followed in the old site if it had not been extruded. It will run, then, 6 fissions, to end at what would have been fs. 17 of the original infection, had the latter continued undisturbed, yielding, then, 3,848x bacilli which, with 409x bacilli which appeared in schedule *a*, initial dose to fs. 9 inclusive, before the extrusion, *makes the total bacilli of the original infection plus the metastasis* 4,257x; with 2,128x units of free immunity over— just what the undisturbed original infection would have yielded. This would be true also, if the 224x bacilli separated into two or more groups, each group setting up successfully its own metastatic focus.

(*7*) Tables 2 and 5, taken together, indicate that extrusion and successful metastasis of the extruded bacilli, whether they occur in the presence or absence of immunity, do not increase the total bacillus load of the tissues; for whatever the size of the metastasis and of its descendants, the infection from which it arose becomes depleted to just that extent.

The danger to the infectee of a metastasis consists rather in the whereabouts, in the tissues, of its location. In a short time-lag infectee, the bacilli of the original infection, and of any metastases that may derive from it, may set up small self-limited foci and lesions which do little or no material damage in the tissues most commonly invaded; for example, the pulmonary "active minimal lesions" which heal rather promptly. But even such slight lesions if set up in the central nervous system for example may do many times the damage to the body economy that a like amount of tissue damage could achieve elsewhere. (The lesions of poliomyelitis admirably illustrate this point.)

Likewise, exogenous reinfections, occurring rather late in the course of a long time-lag infection, are likely to be both infrequent and small, relative to the metastases then occurring, having therefore but little numerical influence on the total bacillus load or on the number of foci of infection, unless one or more of such exogenous infections should happen to locate in an area (for example, the central nervous system) where a minimal amount of actual local tissue damage may do a maximal amount of damage to the body as a whole.

Table 5B: The 240x free immunity left over at *c*, fs. 16, is induced by the 506x bacilli of *c*, fs. 13. This 240x immunity then becomes exhausted in quelling 160x bacilli of metastasis *d*, fs. 6, and 80x bacilli of metastasis *e*, fs. 5.

Schedule *c* likewise contributes 100x free immunity to quell 100x bacilli of metastasis *f*, fs. 5. This 100x free immunity is induced by 100x bacilli, constituting part of the 574x bacilli of *c*, fs. 14; which 574x bacilli have induced their

574x immunity just at the time when the 120x bacilli of metastasis *f*, fs. 5, appear.

Note that the total bacilli which would have appeared in schedule *c* if it had not extruded any bacilli at all, also its concurrent and free immunity, show as A, 4,257x bacilli; B, 2,129x concurrent immunity; C, 2,128x free immunity. The schedule *c* totals of the same items, together with those of the three metastases, add up to the same figures, thus:

Schedule *c*	yields A, 3,222x bacilli;	B, 1,604x concurrent immunity;	C, 1,618 S free immunity
Metastasis *d*	465	235	230
Metastasis *e*	305	155	150
Metastasis *f*	265	135	130
The sum of these =	4,257x bacilli	2,129x concurrent immunity;	2,128x free immunity

Again it appears evident that the occurrence of metastases does not add to the total bacillus load of the tissues but merely redistributes more widely throughout the tissues the total bacillus load existing at each fission.

It may be possible that the concurrent immunity of schedule *c* might be diverted to reduce or end a metastasis, before the free immunity of schedule *c* appears. But again such a diversion of concurrent immunity would not affect the size of the total bacillus load; for schedule *c*, thus depleted of some of its concurrent immunity, would reproduce more bacilli; and more by exactly the same number of bacilli as that number by which the bacilli of the metastasis is reduced by the concurrent immunity transferred from *c*.

This is just as true in the later stages of a long time-lag infection as in its early stages; but its *relative* effects will be far less at later stages than at early stages; because of the great numbers of total living bacilli and of concurrent immunity units which the original infection will by that time have attained.

For example: In order to quell completely a 10x metastasis (or a 10x exogenous reinfection) which happens to occur at the date of fs. 9, of table 4 schedule *c*, this fs. 9 must part with 10x (25 per cent) of its 40x concurrent immunity units.[11]

So also to quell similarly a 10x metastasis (or a 10x exogenous reinfection) which occurs at the date of fs. 30, of table 7, schedule *a*, this fs. 30 must also part with 10x concurrent immunity. But this 10x is but about 0.0001 per cent of the 9,193,088x concurrent immunity units existing at this fs. 30; 9,193,078x concurrent immunity units still remaining.

The mere fact that metastases occur in the course of an original infection seems to make it unlikely that such transfers of concurrent immunity from the original infection to the metastases (or to exogenous reinfections) can be very common; else metastases (and exogenous reinfections), after concurrent immunity has appeared, would be correspondingly uncommon; while the original infection, thus depleted of its concurrent immunity, would then apparently remain as the chief site of infection and of damage; which, in reality, it relatively seldom does.

Table 6 assumes a series of successful exogenous reinfections, each having an initial dose equal to that of the original infection; the series beginning as early

[11] Table 4, schedule *c*, without this loss, ends at fission 17 with A, 4,257x; B, 2,129x; C, 2,128x: with this loss, it ends at fission 18, with A, 8,309x; B, 4,155x; C, 4,154x; that is, about a 95 per cent increase in each of the totals, A, B, C.

TABLE 6

Illustrative of exogenous reinfection in the presence of concurrent immunity. The original infection, Schedule *a*, is the same as Schedule *c*, table 4; which ends at Fs. 17, with 2128 free immunity units.

Note: In tubercle, granting the fission-intervals to be twenty-four hours, this table would represent the first eighteen days of the combined original infection and the 17 reinfections, each of the same size (1x) as that of the initial dose of the original infection; one such reinfection being added daily. The immunity yielded is such that the combined infection ends, with free immunity enough to prevent continuance of the series.

SCHEDULE *a* (The original infection to which reinfection *b* to *r* are added)		EXOGENOUS REINFECTIONS: A SERIES, 1x, AT EACH FS. OF *a*																	REINFECTION ALONE	COMBINED INFECTION
	a	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*i*	*j*	*k*	*l*	*m*	*n*	*o*	*p*	*q*	*r*		
Initial Dose	1x																		0	1x
Fs. 1	2	1x																	1x	3
2	4	2	1x																3	7
3	8	4	2	1x															7	15
4	14	8	4	2	1x														15	29
5	24	14	8	4	2	1x													29	53
6	40	24	14	8	4	2	1x												53	93
7	64	40	24	14	8	4	2	1x											93	157
8	100	64	40	24	14	8	4	2	1x										157	257
9	152	100	64	40	24	14	8	4	2	1x									257	409
10	224	152	100	64	40	24	14	8	4	2	1x								409	633
11	320	224	152	100	64	40	24	14	8	4	2	1x							633	953
12	440	320	224	152	100	64	40	24	14	8	4	2	1x						953	1,393
13	576	440	320	224	152	100	64	40	24	14	8	4	2	1x					1,393	1,969
14	704	576	440	320	224	152	100	64	40	24	14	8	4	2	1x	0	0	0	1,969	2,673
15	768	704	576	440	320	224	152	100	64	40	24	14	8	4	2	1x	0	0	2,673	3,441
16	656	768	704	576	440	320	224	152	100	64	40	24	14	8	4	2	1x	0	3,441	4,097
Fs. 17	160	656	768	704	576	440	320	224	152	100	64	40	24	14	8	4	2	1x	4,097	4,257
Total	4,257x																		16,183x	20,440x

Fissions 14, 15, 16 and 17 of Schedule *a* and their respective reinfections and Fs. 18 (not shown above, but shown later) are those which supply the final total of the free immunity released at and just after the end of the combined infection.

The end of the combined infection, as shown later occurs at Fs. 18; the total bacilli which have appeared throughout the courses of the original infection and the now 18 reinfections being the 20,440x bacilli appearing, to and including Fs. 17 plus 3,168x bacilli of *Fs. 18 plus 1x of the new reinfection; so the total bacilli appearing, then* disappearing, amount to 23,609x. Total final free immunity existing at "constructive" Fs. 21 = 11.795x units.

For definition of reinfection see table 3—Notes.

in the course of the original infection as possible—at its fs. 1; and continuing as long as possible—until stopped by the immunity elicited by the combined infections.

In reality, such daily exogenous reinfections from contact with infective associates must be extremely rare, as already suggested in table 3.

The outstanding points of interest in table 6 are:

(*1*) The termination of the combined infection as a whole after but one more fission than the original infection would have presented in the absence of any such exogenous reinfections; with the release of so much free immunity that, until the free immunity fades, no further infection can occur, except from initial doses of sizes scarcely conceivable as attainable in nature from exogenous sources.

This outcome may be traced thus: Fs. 17 presents a combined infection of 4,257x living bacilli—a total of living bacilli *at* this one fs. 17 equal to the total bacilli which appear throughout the whole course of *a*, considered by itself. These 4,257x living bacilli then disappear as follows: the combined infection at fs. 14 shows 2,673x living bacilli whose immunogenic units will induce 2,673x immunity units at fs. 17. Similarly 3,441x immunity units appear at fs. 18, elicited by the 3,441x bacilli of the combined infection of fs. 15. The work-out, then is this:

Fs. 17; 4,257x bacilli − 2,673x immunity units = 1,584x to fission yielding fs. 18
Fs. 18; 3,168x + 1x[12] − 3,441x = 0 bacilli, and 272 units
of free immunity left from the 3,441x immunity units induced at fs. 18.

The immunity units provided by fs. 16, 17, 18 become free also as they appear at "constructive" fs. 19, 20 and 21, respectively, leaving the infectee protected by (272 + 4,097 + 4,257 + 3,169) x free immunity units; in all, 11,795x free immunity units.

(It is of interest that, if the above series of 1x exogenous reinfections were replaced by a (wholly incredible) series of 10x exogenous reinfections, the combined infection would have disappeared at fs. 19, leaving a total free immunity of over 117,000x.)

(*2*) As already stated, the occurrence of such daily exogenous reinfections as are above discussed, is highly improbable; one or two only may be reasonably expected. It is easy to see that, since the whole series, whether 1x or 10x each, disappears promptly, any lesser number of such reinfections will disappear likewise.

The chief effects of the above 18 exogenous reinfections of table 6, added to the original infection, are:

1. To add to the 4,257x total bacilli appearing in the one original focus, *a*, 19,352x bacilli in, probably, 18 new foci.
2. To wipe out all these 19 foci completely at fs. 18.
3. To leave a total of 11,795x free immunity at "constructive" fs. 21; to which the original infection has contributed 2,128x units, the 18 reinfections 9,667x units, about 80 per cent of the total.
4. The total bacilli appearing, 23,609x and the final free immunity, 11,795x, are rather less than *a* alone would have yielded, had its initial dose been 6x bacilli; that is, 25,542x bacilli and 12,768x free immunity units.

To secure a general picture of the relationships of early exogenous reinfections in short time-lag persons, compare with each other three infections beginning at the same date, each showing the same size of initial dose 1x bacilli; each infection occurring in a different infectee—thus:

Let the first infection develop in an otherwise "normal" guinea pig; hence in the practical absence of immunity, concurrent or free and without exogenous reinfection. Let the second infection develop in an otherwise normal human who produces immunity as per schedule *c*, table 4, also escaping exogenous reinfection entirely. (Time-lag = 3 fission-intervals.) Let the third infection

[12] This 1x is the new reinfection, *s*, at fission 18.

duplicate the second exactly, except that this second human infectee experiences the 18 reinfections as per table 6. (Time-lag = 3 fission-intervals.)

When compared after the lapse of 21 fission-intervals (in tubercle equal putatively to twenty-one days), the three respective outcomes are found to differ greatly, as follows:

TOTAL BACILLI APPEARED TO DATE OF FS. 21	TOTAL LIVING BACILLI EXISTING AT DATE OF FS. 21	TOTAL FREE IMMUNITY UNITS FINALLY	FURTHER FISSION HISTORY
First 4,194,303x bacilli (guinea pig)	2,097,152x bacilli	0x units	Fissions continue indefinitely to death
Second 4,257x bacilli (human)	0x bacilli	2,128x units	None after Fs. 17
Third 23,609x bacilli (human)	0x bacilli	11,795x units	None after Fs. 18

The *proportionate total* bacilli appearing are about 983 to 1 to 5.5. Therefore, to secure from each of the second and third infections the same number of total bacilli appearing (over 4 million) as the first shows from an initial dose of 1x bacilli the second must show an initial dose of about 983x bacilli; the third a dose of about 178x bacilli for the original infection *a*, table 6, and for each of the 18 reinfections, *b* to *s*, inclusive.

The free immunity yielded from the first infection would, of course, remain none; but from the second and third would become over 2 million x free immunity units each.

Finally, the first would continue to fission indefinitely, (until the death of the guinea pig) as per schedule *a*, table 1; but the other two would show no living bacilli to fission at all, after their respective fs. 17 and fs. 18.

The number of living bacilli which must appear in the tissues (hence the total quotas yielded, each quota being allergenic, immunogenic, pathogenic) before material damage can arise is as yet unknown, for the guinea pig or the human. It is therefore difficult even to guess what lesions, if any, might be detectable as produced by the 4 million x bacilli, yielding 4 million x quotas, of the first infection above discussed.

In a human infectee whose immunity time-lag happened to be as long as 21 fission-intervals, instead of the 3 fission-intervals of schedule *c*, table 4, a 1x bacilli initial dose would have yielded during this time-lag exactly the 4 million x bacilli and other figures shown by table 1, schedule *a*, at its fs. 21. But on the appearance of 1x concurrent immunity at fs. 22 (induced by the immunogenic units of the 1x initial dose), the subsequent fissions of this infection would diverge, progressively lessening, from those of table 1, schedule *a*.

If, as and when extrusion of living bacilli by way of the infectee's discharges begins (coinciding, obviously, with the beginning of his infectiveness to others) such extrusion will reinforce the concurrent immunity in cutting down the bacilli. Since one-half of the total bacilli that appear by fission necessarily disappear in the very process of fissioning, the task of the concurrent immunity is limited to getting rid of the other half, plus the initial dose, in which task extrusion of living bacilli into the infectee's discharges may give material aid: since such

TABLE 7

Illustrating the possible effect on the outcome of an infection (initial dose, 1x bacilli) in a moderately long time-lag infectee, of extrusions of living bacilli into the body discharges, the immunity time-lag used is 4 fission-intervals, making the 1x immunity induced by the 1x bacilli of the initial dose take effect at Fs. 4; the 2x of Fs. 1 at Fs. 5, etc.

Schedule *a* shows concurrent immunity, but no extrusion (only the fissions essential to the illustration are recorded here)

	BACILLI APPEARING		CONCURRENT IMMUNITY		BACILLI TO FISSION
Fs. 4	16x	–	1x	=	15x
Fs. 5	30	–	2	=	28
Fs. 6	56	–	4	=	52
Fs. 7	104	–	8	=	96
Fs. 12	2,144	–	192	=	1,952
Fs. 20	256,016	–	23,488	=	232,528
Fs. 26	9,193,088	–	844,736	=	8,348,352
Fs. 30	100,028,480x	–	9,193,088x	=	90,835,392x
Fs. 50*	over 15.2 trillion x	–	about 1.4 trillion x	=	about 13.8 trillion x: no free immunity yet

Schedule *b* shows concurrent immunity and extrusion

This Schedule *b* is (condensed) Schedule *a*, modified by a continuous series of extrusions, beginning Fs. 12; each extrusion equalling 10 per cent of the fission-crop of the fission at which it occurs.

(only the fissions essential to the illustration are recorded here)

	BACILLI APPEARING		CONCURRENT IMMUNITY		BACILLI EXTRUDED		BACILLI TO FISSION
Fs. 7	104x	–	8		(no extr. yet)	=	96
Fs. 12	2,144	–	192	–	(Extr.) = 214	=	1,738
Fs. 20	54,876	–	13,318	–	(Extr.) = 5,487	=	36,071
Fs. 26†	15,638x	–	90,488		(No bacilli left for extrusion)	=	0 bacilli and (74,850x) free immunity units over

At the time of Fs. 30, the living bacilli to fission of Schedule *a* = over 90 million x with no free immunity, and fission continuing. At this same time, Schedule *b* has shown no living bacilli since Fs. 26; and 395,584x of final free immunity; thus;

Free immunity over from Fs. 26 =	74,850x,	available at	Fs. 26
from Fs. 23 =	105,918	available at Constr.	Fs. 27
from Fs. 24 =	110,332	available at Constr.	Fs. 28
from Fs. 25 =	88,846	available at Constr.	Fs. 29
from Fs. 26 =	15,638	available at Constr.	Fs. 30

Total free immunity available at Fs. 30 = 395,584x free immunity units

* With neither immunity nor extrusion, schedule *a*, Fs. 50 yields over 1.25 quadrillions x bac. (The American trillion, used here, = 10^{12}; the American quadrillion = 10^{15}; the respective figures in British usage are 10^{18} and 10^{24}.)

† On ending at Fs. 26, schedule *b*, if carried out in full, shows: total bacilli = 662,345x; total conc. imm. = 266,761x; total bac. extruded 64,412x; total bac. to fission = 331,172x. Thus, conc. imm. + bac. extr. = 331,173x; and the sum of the last two totals = the tot. bac. (compare, respecting this point, table 4, schedule *c*).

extrusions may apparently reach (in the later stages of long-standing infections) figures of many millions per twenty-four hours. The hugeness of the figures involved makes the presentation of detailed schedules of these later events quite impracticable at the present time; but table 7 illustrates in a condensed form the numerical pattern which arises.

"RANDOM" FACTORS

The numerical considerations above presented form but the skeleton of the "speed of reaction" hypothesis deducible therefrom.

The immense field of tuberculosis data now available, much of it yet uncorrelated with this or other hypotheses, shows tubercle infection varying from infectee to infectee, as if ignoring the restrictions which such a numerical skeleton might appear to impose.

But mole and elephant, guinea pig and giraffe, show literal bony skeletons, basically uniform in structural pattern.

Nevertheless each species shows also immense and very obvious differences in the respective working out of that basic pattern, due largely to variations, themselves largely numerical, relative to size, bulk, shape, proportions, rate and continuity of development, etc. Is it not true that every *individual* of every living species, plant or animal, is *unique* in its general work-out of the *general* pattern which its heredity imposes upon it?

On such variations, recognizable in the whole, but not yet satisfactorily reduced to their final numerical relationships, rest differences between species; also between embryo and adult; between male and female.

Evidently, there are numerical factors which maintain the general pattern, but also numerical factors which permit, even compel, variations in the general pattern.

In relation to tubercle infection, the strict logarithmic schedules of table 1 are numerically modified by extrusion, by metastasis, by exogenous reinfection, by immunity, that is, by "random" factors; since, although they operate numerically, they arise at variable times and in unpredictable sizes, proportions, combinations, sequences, etc. in different infectees.

This leaves each individual infectee (for example, infected with living virulent human type tubercle bacilli) only one "nonrandom" factor in the welter of interplay of the "random" factors—namely, his own individual immunity time-lag, that is, his own genetically derived speed of reaction in response to the immunity-eliciting stimuli of his infection.

But in addition to this endogenous interplay of "biological mechanics," the infectee daily encounters other at least possible exogenous factors in his individual sociological environment, physical and biological. These, in variety, complexity, multiplicity and changefulness, defy numerical analysis. It is exactly when such multiplexes confront the observer that the "control" group serves its best purposes, yielding broad over-all conclusions where minute detailed data are lacking.

In regard to tubercle infections, the human population shows two primary groups, the infected and the noninfected, each constituting a "water-tight" control for the other.

After long centuries, rather millenia, the single differential factor is now recognized; broadly, the presence of the tubercle bacillus in the former, its absence in the latter, eliminating wholly all other conceived or conceivable differentials.

Under separate consideration, the infected group itself resolves also into two mutual control groups; one, a majority group (perhaps 75 per cent of the total infectees) which shows no material damage; and the 25 per cent (?) remaining minority group, which does show *material damage*.

Both show infection; therefore infection is not the *sought-for differential*.

Both show immunity; immunity *per se* therefore is not the sought-for differential.

Both show marked quantitative differences in the amount of immunity attained, the 75 per cent who escape material damage showing little immunity production, the 25 per cent who show material damage showing also much immunity production; therefore, the quantity of immunity produced is not the sought-for differential. (If it were, the incidence of material damage on the two groups would be exactly reversed; the 75 per cent would show the damage, the 25 per cent would escape.) Both show extrusions, metastases, reinfections, "allergy," etc. This again leaves the immunity time-lag as the one clean-cut differential between these two groups.

Just so with such factors as "colds," measles, puberty, adolescence—or broadly, the "strains of life" on the one hand; sunlight, fresh air, good nutrition, etc. on the other; until one or more of these items can be shown *to be confined*, qualitatively or quantitatively or both, to the one group, the 75 per cent, or to the other group, the 25 per cent, they cannot earn a *differential status either as preventives* or as precipitants of material damage.

Factors that contribute to exposure to infection contribute very definitely to the incidence of infection; but by no means are they further necessary to the precipitation of cases in the thus-infected.

For example, about 70 per cent, as a general rule, of the initially tuberculin-negative entrants to medical and nursing courses become infected during their first year in course.

The majority of these infectees continue and finish their courses, showing no (or no material) damage. Does this majority escape "colds," and other "strains of life" or enjoy more sunlight, fresh air, etc. than the minority who do show material damage?

SUMMARY

The natural course of a tubercle infection of guinea pig or person (with living virulent human type bacilli) is pictured in seven simple numerical tables as a rising tide of bacilli which, unless checked by antibacterial immunity, inevitably reaches, sooner or later, numbers great enough to precipitate, through their pathogenic products, material damage enough to constitute a "case," going on to a fatal ending.

This latter is the natural course of such an infection in normal guinea pigs. *In* contrast, most human North American white infectees (92 per cent?) respond

sooner or later with antibacterial immunity units, to the immunity-eliciting stimuli (immunogenic units) produced by the infecting bacilli.

The *immunogenic* units, being released by the bacilli, one unit from each bacillus, increase in number as the infection advances; which numbers therefore increase exactly in correspondence with the increases in the numbers of the bacilli. But the *immunity* units which the immunogenic units thus elicit from responsive tissues (each immunogenic unit inducing one immunity unit) depend for the *time* of their appearance, as actively functioning antibacterial agents, upon the particular speed with which the particular infectee's tissues may react to the immunogenic stimuli they receive.

In the guinea pig this speed of reaction is invariably so slow that the time-lag between the immunogenic stimulus and the immunity response is too great to permit the appearance of sufficient immunity to check materially a virulent infection before fatal damage has already been done.

Human infectees, unlike the guinea pig, vary in their speeds of reaction from infectee to infectee. Only perhaps 8 per cent of North American whites have such long immunity time-lags as *all* guinea pigs show. These, like the guinea pigs, die, unless aided by some form of antibacterial therapeusis.

Of the remaining 92 per cent (?) human infectees, the majority inherently possess such short immunity time-lags (that is, such rapid speeds of reaction) that a (small) antibacterial immunity appears early, hence while the bacilli are relatively few; the infection being thus ended early, with little or no serious damage.

Just so, one gallon of water may extinguish an incipient fire, *if* it is applied *early*; whereas thousands of gallons may fail to put out the fire if not applied until later.

The remaining minority, perhaps 15 to 20 per cent of the total human infectees, possess somewhat longer time-lags; therefore material damage is done by the relatively huge numbers of bacilli which have appeared before substantial immunity appears. But those huge numbers of bacilli induce in due time equally huge numbers of immunity units; thus ultimately quelling the infection, which therefore ends in recovery.

The seven tables illustrate the numerical details of the various processes above outlined; dealing with single infections, metastases, reinfections, etc. in the *absence* of immunity, and in its *presence*.

SUMARIO

La evolución natural de una infección tuberculosa en cobayos o personas (con bacilos virulentos vivos de tipo humano) aparece reproducida en siete tablas númericas como una marea alta de bacillos que, a menos que sea contrarrestada por la inmunidad antibacteriana, alcanza, tarde o temprano, inevitablemente magnitud suficiente para provocar con sus productos patógenos daños materiales que bastan para formar un "caso" que prosigue hasta un desenlace fatal.

Esto último representa la evolución natural de una infección de esa naturaleza en los cobayos normales. En contraposición, la mayor parte (92%?) de los sujetos blancos norteamericanos infectados responden, tarde o temprano, con

unidades de inmunidad antibacteriana a los estímulos inmunógenos (unidades inmunógenas) que producen los bacilos infectantes.

Las unidades inmunógenas liberadas por los bacilos, una unidad por cada bacilo, aumentan a medida que avanza la infección y exactamente en proporción al aumento del número de bacilos. Sin embargo, las unidades de inmunidad que las unidades inmunógenas fomentan en los tejidos propicios (correspondiendo a cada unidad inmunógena una unidad de inmunidad) se gobiernan, en cuanto al momento de su aparición como elementos antibacterianos en función activa, por la celeridad con que los tejidos del sujeto dado reaccionen a los estímulos inmunógenos que recibe.

En el cobayo la velocidad de la reacción es invariablemente tan lenta que el tiempo trascurrido entre el estímulo inmunógeno y la respuesta inmunizante es demasiado largo para permitir la aparición de una inmunidad suficiente para cohibir efectivamente una infección virulenta antes de que produzca lesiones letales.

En oposición al cobayo los sujetos humanos infectados varían en la velocidad de su reacción, y quizás solamente 8% de los blancos norteamericanos muestran un tiempo de inmunidad tan largo como el que revelan todos los cobayos. Esos sujetos mueren, en igual forma que los cobayos, a menos que los fortalezca alguna terapeútica antibacteriana.

Del 92% (?) restante de seres humanos infectados, la mayoría posee inherentemente un tiempo inmunológico tan breve (es decir una reacción tan rápida) que la inmunidad antibacteriana se presenta tempranamente y por eso los bacilos son relativamente pocos, de manera que la infección termina prontamente y apenas produce o no produce lesiones graves. Este es el mismo principio conforme al cual un balde de agua apagará un incendio incipiente si se usa tempranamente, en tanto que millares de baldes tal vez no lo apaguen si se espera demasiado tiempo.

La minoría restante, quizás 15 a 20% del total de sujetos infectados, muestran reacciones menos rápidas, por lo cual produce lesiones importantes la cantidad relativamente enorme de bacilos presentes antes de desarrollarse una inmunidad sustancial, aunque esa enorme cantidad de bacilos también da origen con el tiempo a una cantidad igual de unidades de inmunidad, erradicando así por fin la infección que termina por consiguiente en la reposición.

Las siete tablas ponen de manifiesto los pormenores numéricos de los varios procesos bosquejados, discutiendo las infecciones aisladas, metástasis, reinfecciones, etc., en ausencia y en presencia de inmunidad.

REFERENCES

(1) Hill, H. W.: The epidemiology of "human" bacillus tuberculosis in the human, Bull. British Columbia Bd. Health, Victoria, B.C., Canada; Installments: 1, May, 1941; 2, June, 1941; 3, 4, 5, November, 1941; 6, 7, April, 1942; 8, June, 1942; 9, November, 1942; 10, 11, February, 1943; 12, March, 1943. (References to the cognate general literature are included.)

(2) Hill, H. W.: "Speed of reaction" hypothesis: Its numerical foundations in respect to the tubercle bacillus, Am. Rev. Tuberc., 1944, *49*, 414.
(3) Hill, H. W.: "Hanging-block" preparations for the microscopic observation of developing bacteria, J. Med. Research, March, 1902, *7*, no. 2 (New series, vol. II, no. 2); January, 1902.
Also Boston (Mass.) Board of Health Laboratory Reports, on bacterial fission, 1901, 1902.
(4) Hill, H. W., and Rickards, B. R.: Notes on morphology, Proc. Am. Pub. Health A., 30th annual meeting, 1903.

ELECTROCARDIOGRAMS IN CHRONIC PULMONARY DISEASE[1]

A Theoretical Interpretation

EMANUEL GOLDBERGER[2] AND SIDNEY P. SCHWARTZ

The electrocardiographic patterns in chronic pulmonary disease, including pulmonary tuberculosis, vary widely and many attempts have been made to explain the changes observed (1, 2, 3, 4, 5, 6). For example, in one of the more recent reviews of the subject (3), the electrocardiographic changes observed in pulmonary tuberculosis were ascribed to one or more of the following four factors: (*a*) changes due to independent heart disease; (*b*) changes due to the liberation of (hypothetical) toxic substances from the tuberculous process; (*c*) changes due to the impaired pulmonary circulation and the resultant cor pulmonale; (*d*) changes due to the position of the heart.

In recent papers (8, 10, 20) we emphasized the importance of the position of the heart as a cause of changes in the standard lead patterns. Since then we have extended our observations. Inasmuch as cases of chronic pulmonary disease lend themselves admirably to our method of analysis, our results, will be presented principally from this point of view.

MATERIAL AND METHOD

A total of 125 cases of chronic pulmonary disease was studied. These cases were selected from the wards of the Medical and Pulmonary Divisions of Montefiore Hospital and from the Department of Medicine, Lincoln Hospital. Of this group there were 75 with pulmonary tuberculosis and 50 with nontuberculous conditions such as bronchial asthma, emphysema, bronchiectasis and cancer of the lung.

In most of these cases, in addition to the standard and precordial leads, multiple unipolar leads were taken (9). As a means of control, we compared the records so obtained in this series with our findings in a group of 100 normal subjects in whom similar records were taken.

We believe that the electrocardiographic patterns observed in the standard leads, not only in cases of chronic pulmonary disease but in all cases, normal and abnormal, depend on two factors: (*1*) variations in the position of the heart; (*2*) the basic electrocardiographic patterns obtained from unipolar leads taken directly over or near the surface of the heart.

VARIATIONS IN THE POSITION OF THE HEART

Our entire concept of what is meant by "the position of the heart" is much more extensive and inclusive than that of the earlier investigators. In the first place, the heart may rotate around any one or more of the following three axes:

[1] From the Medical Division and the Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases, New York, New York.

[2] Work done under a Fellowship of the Martha M. Hall Foundation, Montefiore Hospital for Chronic Diseases.

1: Rotation around an antero-posterior axis (figure 1a). When this occurs, the long axis of the heart becomes more horizontal or more vertical.
2: Rotation of the heart around its long axis (figure 1b). When this occurs, the apex of the heart may rotate posteriorly. This has been described as a clockwise type of rotation. In such a case, the right ventricle rotates more anteriorly to the left. On the other hand, the apex of the heart may rotate anteriorly and the right ventricle more to the right. Such rotation is called counter-clockwise rotation. Clockwise rotation of the heart around its long axis is ordinarily, but not necessarily, associated with a vertical position of the heart. When the heart lies horizontally, there is usually some degree of counter-clockwise rotation of the heart around its long axis. These two types of rotation

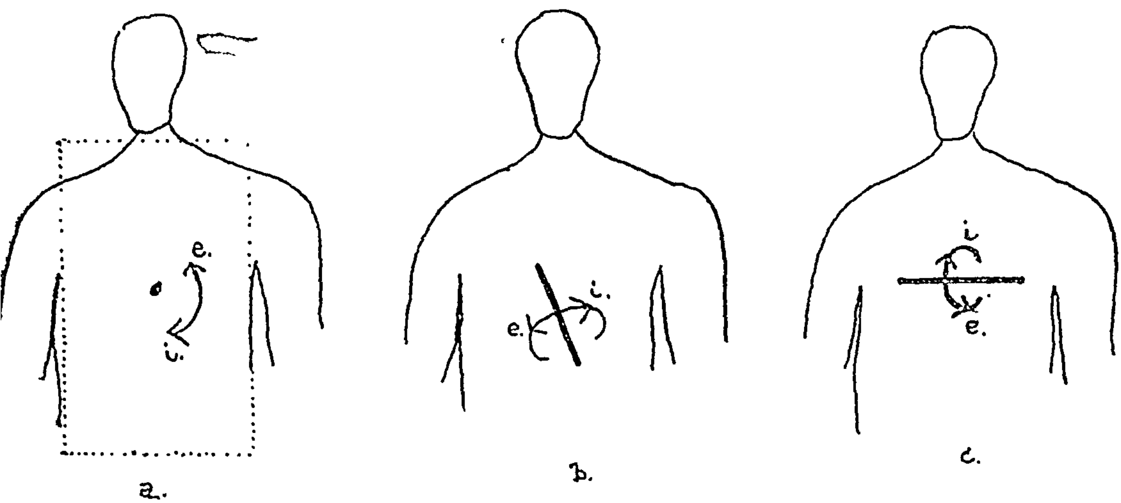


FIG. 1. The axes around which the heart can rotate.
a. Antero-posterior axis. The arrows show the directions in which the apex of the heart can move. During inspiration (i), the apex moves downward. During expiration (e) it moves upward. The dotted rectangle shows the frontal plane of the body. The antero-posterior axis, as can be seen, points in a direction perpendicular to the frontal plane.
b. The long axis of the heart. The arrows show the directions in which the heart can rotate. During inspiration (i) the right ventricle is more anterior. During expiration (e) the right ventricle rotates to the right.
c. The transverse axis. The apex of the heart can move anteriorly or posteriorly. During respiration there appears to be anterior rotation around this axis.

are well known, yet it is not generally recognized that the heart may rotate around another axis, namely,
3: Rotation around a transverse axis (figure 1c). When this occurs, the apex of the heart is displaced forward; or the apex is displaced backward.

From what we have just said, it is obvious that there are numerous positions that the heart may occupy, even without being displaced into the right or left chest. Fortunately it is not necessary to study all possible combinations. For patients with chronic pulmonary disease, we need emphasize only the following positions: the vertical heart, with clockwise rotation around its long axis, and with forward rotation of the apex; the vertical heart in which the apex has been displaced backward, and the horizontal heart.

THE BASIC ELECTROCARDIOGRAPHIC PATTERNS OF UNIPOLAR LEADS NEAR THE SURFACE OF THE HEART

Although the usual analysis of standard lead patterns in the electrocardiogram is by means of axis deviation, we can make use of the following simple nonmathematical method, namely: *When the basic electrocardiographic patterns of unipolar leads taken directly over or near the surface of the right and of the left ventricles are known and when similar patterns are found at points distant from the heart, such as the extremities, we can assume that the patterns found on the surface of the heart are being transmitted to the extremities.*

In this connection it is obvious that the basic pattern of a normal heart will be completely different from the basic electrocardiographic patterns obtained, for example, in cases of myocardial infarction. However, for the purposes of this paper we need only consider the basic electrocardiographic patterns of the normal heart and in right ventricular hypertrophy.

By means of unipolar leads (8, 16, 20) we have determined the basic electrocardiographic patterns which are found over the surface of the right ventricle and over the surface of the left ventricle. However, before we describe these basic patterns we should like to define what is meant by unipolar leads. The ordinary standard and precordial leads in use are bipolar leads because they record the difference between the potentials of two points on the body; a unipolar lead actually records the potential from any one point on the body (16). Since this is so, the standard leads are different from the actual unipolar leads obtained from the left arm, the right arm and the left leg. However, our method of analysis is applicable to standard leads because the following relationships hold between the standard leads and the unipolar extremity leads:

Lead I is usually similar to the unipolar lead from the left arm.
Lead III is usually similar to the unipolar lead from the left leg.
Lead II equals the sum of leads I and III.

The basic QRS pattern over the right ventricle, as recorded in unipolar precordial leads V_1 and V_2[3] consists of a small r and a deep S (rS). There may or may not be a final r (figure 2). T is upward but may be downward. This pattern occurs both in the normal heart and with right ventricular hypertrophy and left ventricular hypertrophy.

When the right ventricular hypertrophy becomes very marked, this pattern changes. In such a case, a high R wave is seen in precordial leads V_1 and V_2. This may be preceded by a small r and s (figure 2e). T tends to be downward. We are not yet able to state what degree of right ventricular hypertrophy must be present to cause this or how many other factors are involved. In this connection, we can also point out that similar patterns may be seen in cases of right

[3] Lead V_1 is the unipolar precordial lead taken with the chest electrode on the fourth intercostal space just to the right of the sternum. Lead V_2 is taken with the electrode on the fourth intercostal space just to the left of the sternum (9).

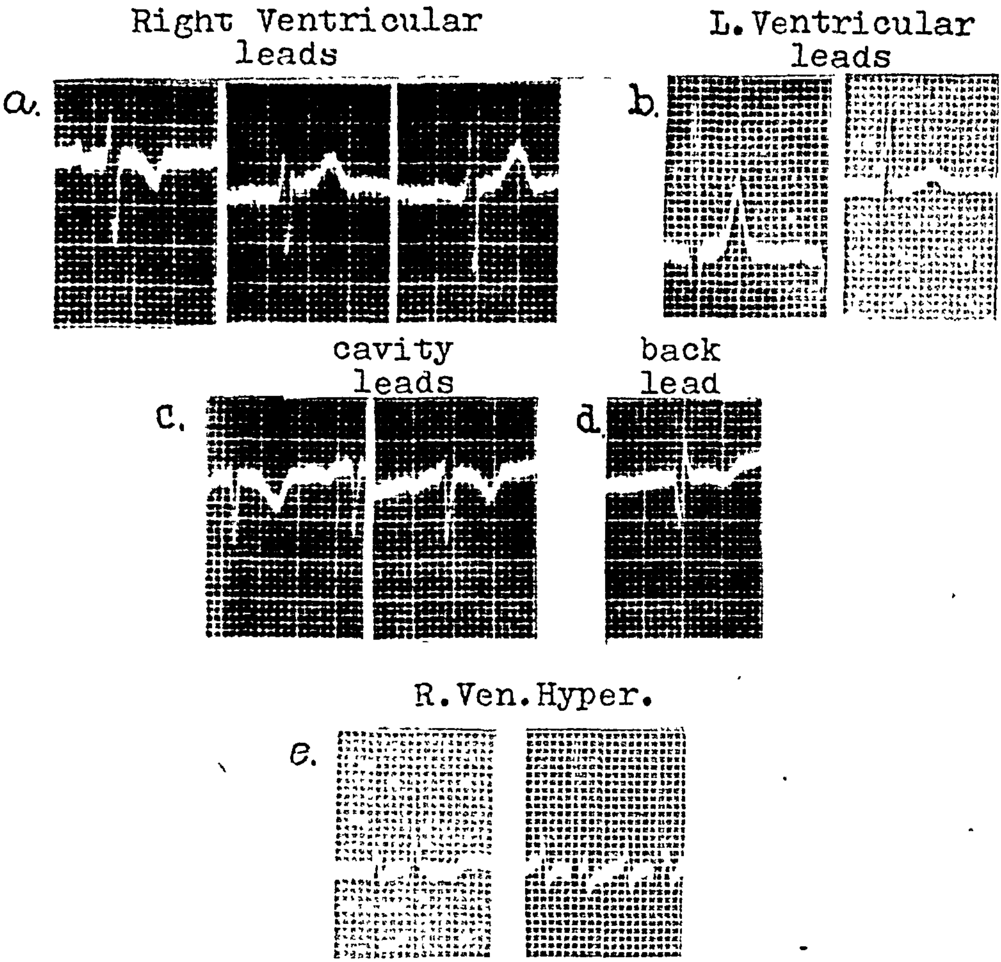


FIG. 2. The basic unipolar lead patterns found near the heart.

a. Right ventricular leads. The three records show precordial leads which can be obtained from the right and left side of the sternum at the level of the fourth intercostal space. Such a pattern occurs normally and also in cases of right ventricular hypertrophy.

b. Left ventricular leads. The two records show typical patterns which can be found in precordial leads near the region of the apex of the heart.

c. Cavity leads. The two records show patterns obtained from leads which face the interior of the heart. These particular tracings were obtained from leads taken over the right upper chest wall.

d. Back lead. This shows the basic pattern obtained from a lead on the mid-back.

e. R. Ven Hyper.: The two records show the effect of marked right ventricular hypertrophy on precordial leads near the sternum. However, right ventricular hypertrophy may exist with a normal pattern in these leads. Notice also the biphasic P waves. In the second record, auricular flutter is present.

bundle branch block (12), which has been considered by some as one of the factors helping to cause this pattern (17).

The basic pattern over the left ventricle, as in precordial leads V_4 and V_5 and

V_6,[4] consists of a small initial q wave followed by a tall R wave (qR) (figure 2b). There may or may not be a final S wave. T is usually upright. This pattern occurs both in the normal heart and in right and left ventricular hypertrophy. With marked right ventricular hypertrophy, the R wave may be quite small.

The heart also has an endocardial surface, from an electrocardiographic standpoint. The basic unipolar lead from within the heart consists of a deep downward deflection with a downward T (figure 2c). If the electrode faces the right side of the interventricular septum, the downward deflection is preceded by a small r wave (20) (figure 2c).

There is one other basic pattern from unipolar leads near the heart that is important. If the electrode is placed over the auricles, (as in an esophageal lead) or on the back in the interscapular region, the basic pattern will consist of a deep Q, a high R and a downward T (20) (figure 2d). This is due to the fact that the electrode is facing both the endocardial and epicardial surfaces of the heart, especially of the left ventricle.

RESULTS

With these facts, we can study the effect that variations in the position of the heart have on the standard leads.

The vertical heart: When the heart is vertical the left ventricle lies over the diaphragm and faces the left leg. The left leg lead and lead III, therefore, record a qR pattern. The right and left arms tend to face the cavity of the heart and tend to have a downward deflection. However, since clockwise rotation of the heart around its long axis is usually present in a vertical heart, the left arm may face the right side of the interventricular septum or even part of the surface of the right ventricle. When this occurs, the left arm lead and lead I will have an rS deflection. Such a pattern is ordinarily described as right axis deviation. Figure 3 illustrates two such cases. Figure 3a is the record of a normal subject. Figure 3b is the record of a patient with chronic pulmonary tuberculosis involving the right lung. Table 1 shows the incidence of this pattern both in the normal subjects and in the cases with chronic pulmonary disease in our series.

In the normal subject the vertical heart causes the left ventricle to face the left leg, as we have pointed out above. With moderate or even marked right vetricular hypertrophy the heart usually lies vertically and the left ventricle also faces the left leg. Inasmuch as the occurrence of right ventricular hypertrophy does not ordinarily alter the basic electrocardiographic patterns of the right and left ventricles, there is no way of determining electrocardiographically the presence of a moderate degree of right ventricular hypertrophy.

[4] Precordial lead V_4 is taken with the electrode on the left midclavicular line at the level of the fifth intercostal space. Lead V_5 is taken at this same level on the left anterior axillary line. Lead V_6 is also taken on this same level, but on the left midaxillary line. It should be pointed out that, if clockwise rotation of the heart around its long axis occurs, leads V_4 and V_5 and even V_6 may face the right ventricle principally.

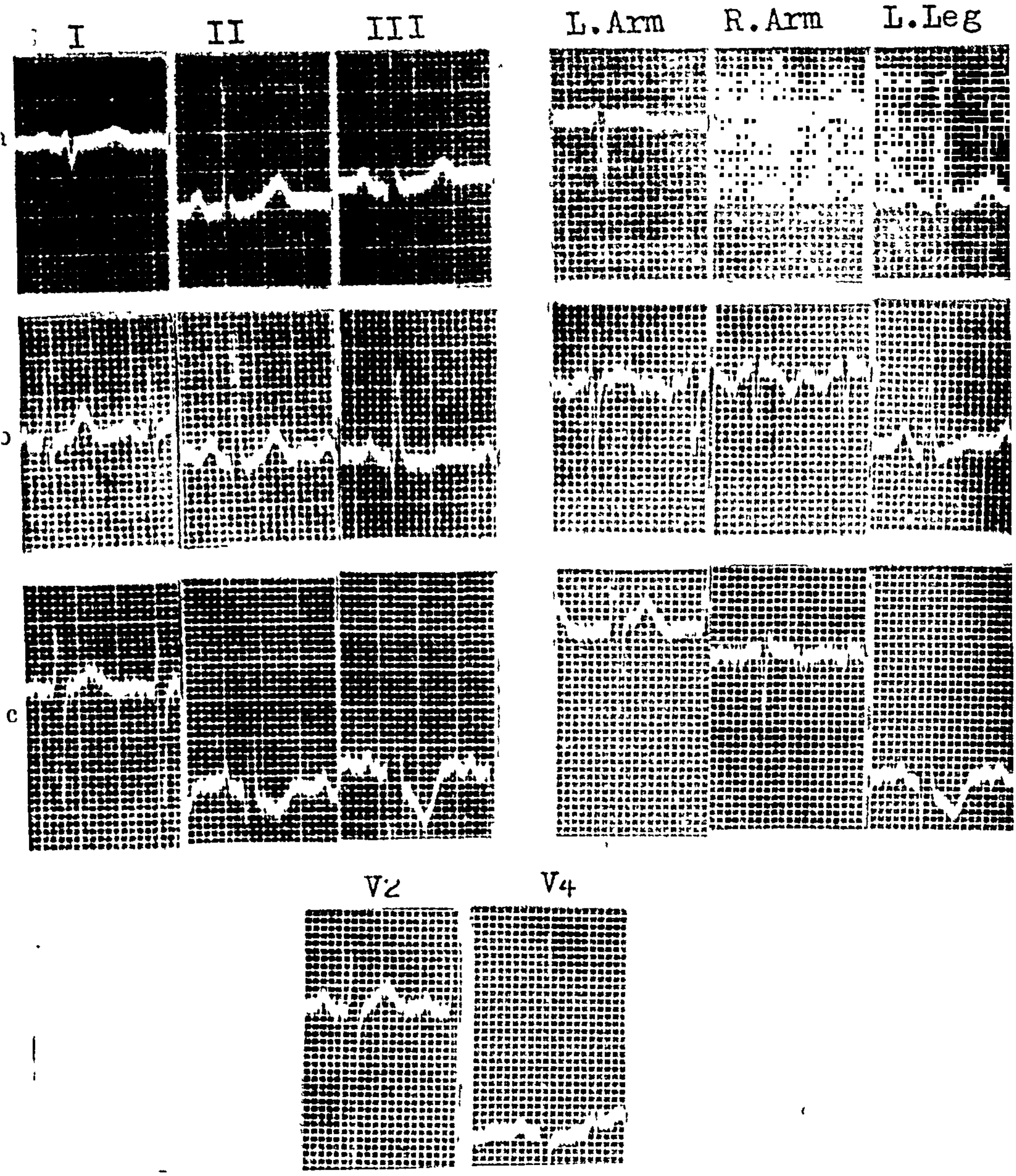


FIG. 3. The electrocardiogram of a vertical heart. I, II, III are standard leads. L. Arm, R. Arm, and L. Leg are unipolar leads from the left arm, the right arm and the left leg (9).
a. Normal subject. J. P., male, 25.
b. Case of chronic right pulmonary tuberculosis. S. A., male, 27.
c. Case of pulmonary tuberculosis, right thoracoplasty and hypertensive cardiovascular disease. M. G., female, 43. V_2 and V_4 are precordial leads.

Even with left ventricular hypertrophy, if the heart is vertical, the same pattern occurs. Figure 3c illustrates such a case, that of a 43 year old woman

with hypertension and left ventricular hypertrophy in addition to pulmonary tuberculosis, for which a right thoracoplasty had been performed. Notice the similarity between the left arm lead and lead V_2; and the similarity between the left leg lead and lead V_1. However, in the ordinary case of left ventricular hypertrophy the heart does not lie vertically and this pattern is not observed.

The vertical heart with the apex rotated backward: In cases of chronic pulmonary disease an unusual pattern is occasionally encountered in the standard leads. This consists of a downward QRS in the three standard leads (10, 11). Such a pattern may, however, be observed in a normal heart (10, 18, 19). This pattern

TABLE 1

The incidence of electrocardiographic patterns in our normal cases and in our cases of chronic pulmonary disease

	R.A.D.[1] VERTICAL HEART	R.A.D.[2] DOWNWARD T WAVES	INDETERMINATE[3]	L.A.D.[4] HORIZONTAL HEART	L.A.D.[5] DOWNWARD T WAVES	S WAVES[6] APEX BACKWARD	TOTAL
Normal..............	24 (24%)	5 (5%)	25 (25%)	40 (40%)	1 (1%)	5 (5%)	100
Chronic pulmonary disease............	44 (35%)	7 (5%)	19 (15%)	38 (30%)	7 (5%)	13 (10%)	125

[1] R.A.D.: Right axis deviation. This is due to a vertical position of the heart.

[2] Forward rotation of the apex of a vertical heart can cause the T waves in the left leg lead and leads II and III to point downward.

[3] Indeterminate: These electrocardiograms showed characteristics of both right and left axis deviation.

[4] L.A.D.: Left axis deviation. This is due to a horizontal position of the heart.

[5] Counter-clockwise rotation of a horizontal heart around its long axis can cause the T waves in the left arm lead and lead I to point downward.

[6] When the apex of the heart is rotated backwards, prominent S waves may appear in the three standard leads. There is no description of this pattern in terms of axis deviation.

does not correspond to any of the criteria of axis deviation, but as we have mentioned elsewhere (10) the explanation for such a pattern is very simple if we assume that in such cases the heart lies vertically and the apex has been rotated backward.

When this happens, the left leg, which ordinarily faces the left ventricle in a vertical heart, would tend to face the right ventricle. Its pattern would therefore change from a qR deflection to an rS deflection, as would lead III. Similarly both the right and left arms would tend to face the back of the heart, because with the backward displacement of the apex, the base of the heart is pushed forward. The basic pattern posteriorly, as we mentioned above, is a QR pattern. It is always seen in the right arm lead in these cases (10), but may not be seen in the left arm lead. This indicates that clockwise rotation of the heart around its long axis is also present. Figure 5a illustrates such a case. This is the record

of a 29 year old male who had attacks of bilateral spontaneous pneumothorax and who later developed acquired cystic disease of the lungs.

Even if the apex is not pushed this far back and the left ventricle still faces the left leg, the right arm tends to face the back of the heart and records a QR pattern. In the standard leads this is noted by the fact that lead II has an rS pattern like lead I, whereas in the ordinary case with a vertical heart lead II tends to resemble lead III (16). We found a QR pattern in the right arm lead, similar to that shown in figure 5a, in 5 per cent of our normal cases, and in 10 per cent of our cases with chronic pulmonary disease. (See table 1.) However, in the pulmonary cases the QR pattern in the right arm lead was usually quite marked. (Compare figure 5c with figure 5a.)

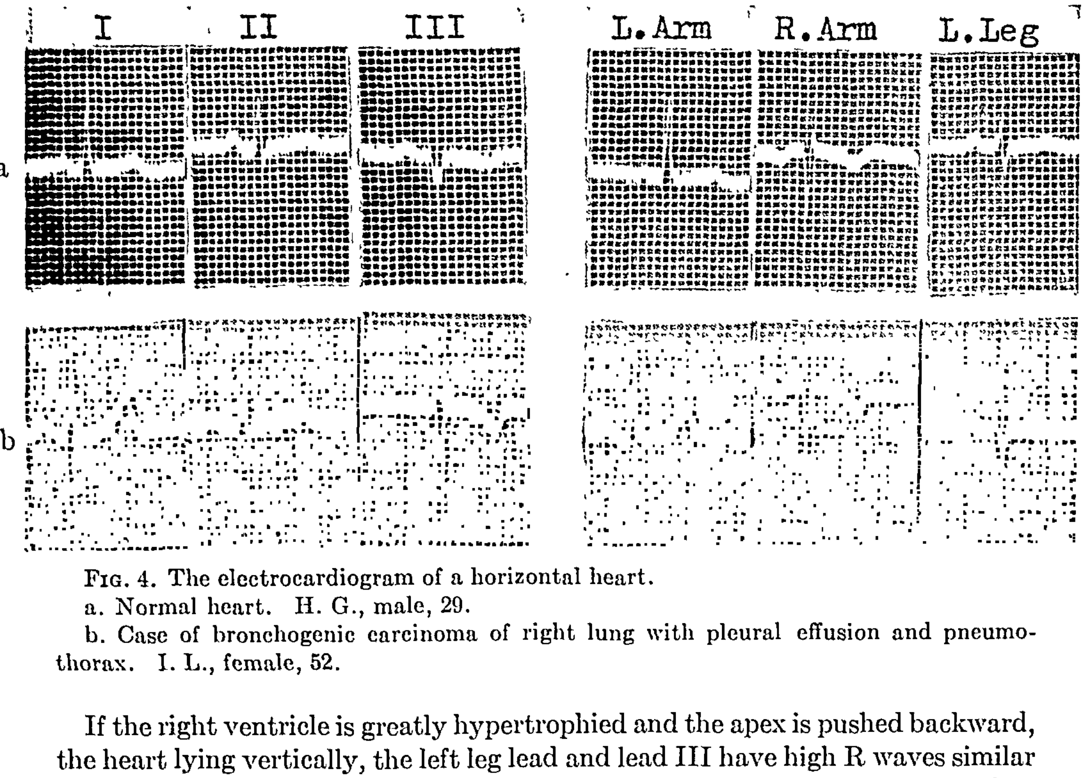


FIG. 4. The electrocardiogram of a horizontal heart.
a. Normal heart. H. G., male, 29.
b. Case of bronchogenic carcinoma of right lung with pleural effusion and pneumothorax. I. L., female, 52.

If the right ventricle is greatly hypertrophied and the apex is pushed backward, the heart lying vertically, the left leg lead and lead III have high R waves similar to the pattern found in precordial leads V_1 and V_2. However, in such records a Q wave will be missing in the left leg lead and lead III (20). Figure 5b illustrates such a pattern. This is the record of a 48 year old woman with chronic bronchitis, emphysema and right heart failure.

The horizontal heart: When the heart is horizontal the left ventricle faces the left arm and the left arm lead and lead I have a qR pattern. The right ventricle faces the left leg, and the left leg lead and lead III show an rS pattern. Figure 4a illustrates this in a normal subject; figure 4b, in a patient with right sided bronchogenic carcinoma, pneumothorax and pleural effusion. The incidence of this

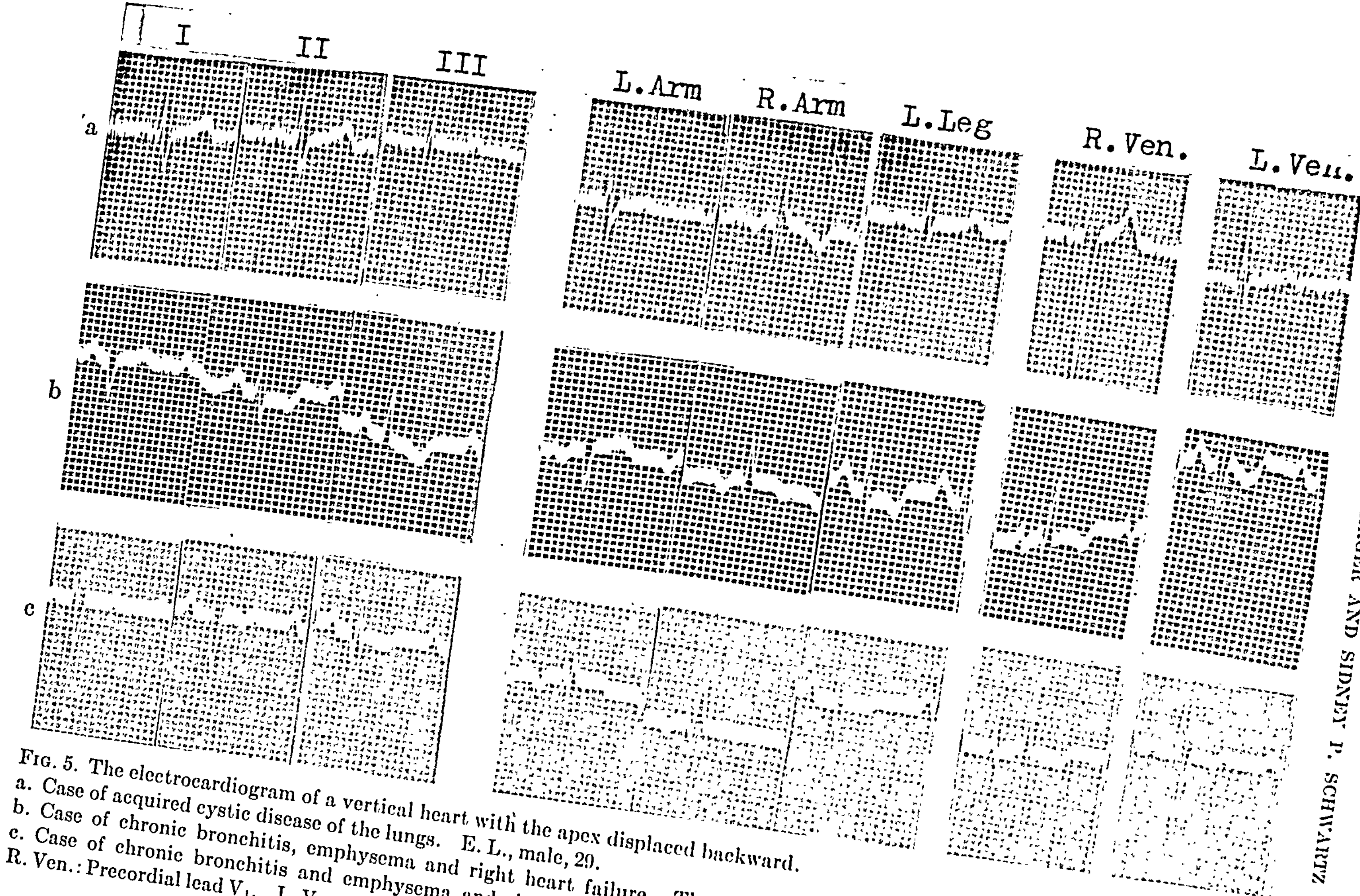


FIG. 5. The electrocardiogram of a vertical heart with the apex displaced backward.
a. Case of acquired cystic disease of the lungs. E. L., male, 29.
b. Case of chronic bronchitis, emphysema and right heart failure. The patient had received digitalis. E. C., female, 48.
c. Case of chronic bronchitis and emphysema and right heart failure. The patient had received digitalis. K. R., male, 66.
R. Ven.: Precordial lead V_1. L. Ven.: Precordial lead V_6 (figures 5a, c) and V_4 (figure 5b).

pattern in our series is shown in table 1. Such a pattern ordinarily is described as left axis deviation. It occurs both in a normal horizontal heart, in a horizontal heart in which left ventricular hypertrophy occurs and in a horizontal heart with right ventricular hypertrophy, provided the basic electrocardiographic patterns have not changed. If the right ventricular hypertrophy has a basic pattern of the type shown in figure 2e, the left leg lead and lead III have high R waves, and left axis deviation does not occur, even though the heart is horizontal (8).

We may point out that when the apex of a horizontal heart, whether or not it is normal, is displaced backward, the right arm lead records a QR pattern just as in the case of the vertical heart whose apex was displaced backward. This causes lead II to resemble lead III instead of resembling lead I (16).

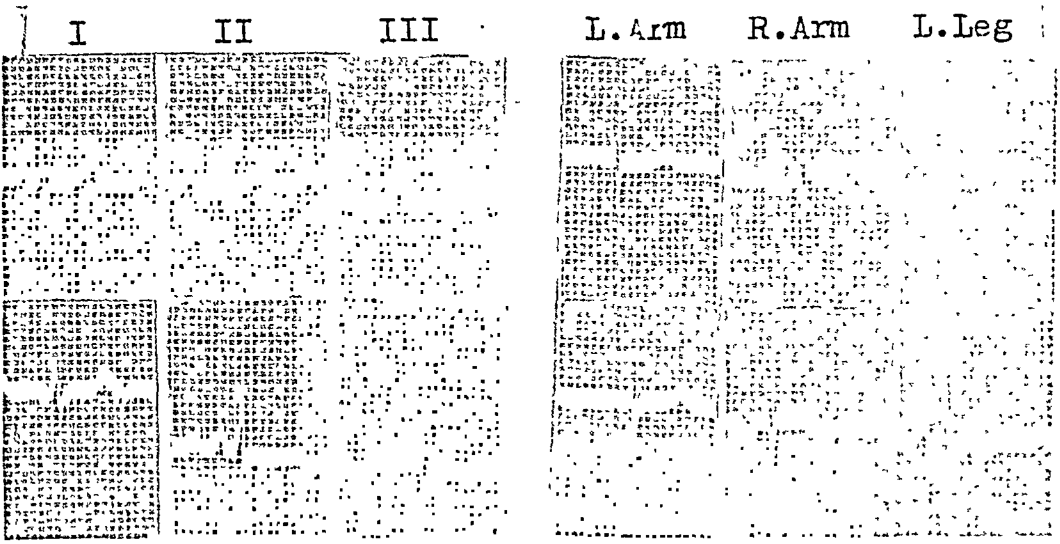


FIG. 6. The effect of respiration on the electrocardiogram of a vertical heart Normal heart. P. C., female, 19.

Control (upper line)—taken during quiet respiration.

Inspiration (lower line)—taken during a deep inspiration.

Both records were taken with the patient in a recumbent position.

T wave changes in vertical hearts: So far we have stressed the changes in the QRS complex which are caused by changes in the position of the heart. Although these facts have been partially known in the past, it was felt by many that, if right axis deviation was merely due to a vertical heart, the additional presence of a downward $T_{2,3}$ indicated right ventricular hypertrophy, enlargement or right ventricular strain (3). This, is not so, because in a vertical heart a combination of forward rotation of the apex around the transverse axis of the heart and clockwise rotation of the heart around its long axis can cause the T waves of the left leg lead and of leads II and III to point downward. Figure 6 illustrates how this can occur in a normal individual. This is the record of a 19 year old girl. Fluoroscopy of the chest showed that she had a normal vertical heart. The electrocardiogram taken during quiet respiration showed a qR in

the left leg lead and leads II and III, indicating that her heart was vertical. On deep inspiration, however, the T wave of the left leg lead became downward, and in leads II and III similar changes were noted. When the patient stood, similar changes also occurred. This is a common observation in patients with normal vertical hearts (14) although, in our cases of chronic pulmonary disease, the associated emphysema which was so often present and the low diaphragm allowed very little respiratory changes to be noted in the electrocardiogram. However, figure 7 illustrates similar changes in a patient with chronic asthma and emphysema. Here, again, postural changes (not shown) were similar.

As a matter of fact, a downward T in the left leg lead was seen in 15 per cent of our normal cases who showed right axis deviation. When the downward T

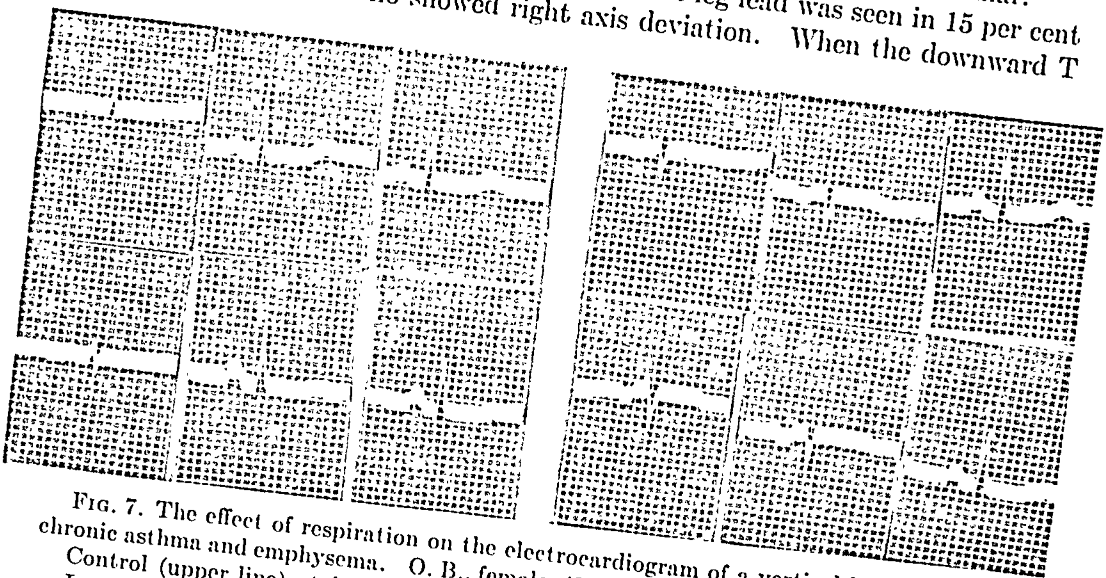


FIG. 7. The effect of respiration on the electrocardiogram of a vertical heart. Case of chronic asthma and emphysema. O. B., female, 48.
Control (upper line)—taken during quiet respiration.
Inspiration (lower line)—taken during a deep inspiration.
Both records were taken with the patient in a recumbent position.

is not marked, T_2 may point upward although T_3 is downward. Table 1 shows the incidence of downward T waves in our series. There is another way of proving that these T wave changes are due to rotation of the heart. As we mentioned above, when the heart lies vertically, there is usually some degree of associated clockwise rotation of the heart around its long axis. Inspiration and standing, which cause the heart to lie more vertically, increase the clockwise rotation and cause forward rotation of the apex around the transverse axis of the heart. If this is so, and if the downward T wave changes are due to rotation of the heart, it should be possible in a case where the heart is vertical, irrespective of how the T waves in the left leg lead and leads II and III point, and irrespective of what the effects of inspiration are, to find both upward and downward T waves in the region of the left leg lead. It should also be possible in a case where the heart is horizontal, irrespective of how the T waves of the left

arm lead and lead T point, and irrespective of what the effects of inspiration are, to find both upward and downward T waves in the region of the left arm lead.

In order to test the validity of this hypothesis, we selected at random, 47 cases, including 25 cases where the heart was vertical, using the following rules. The vertical cases included 10 normal subjects and 15 with chronic pulmonary disease.

Rule 1: To determine the effect of forward rotation of the apex around the transverse axis of the heart:

(a) Place the right arm electrode anteriorly and lower.
(b) Place the left arm electrode anteriorly and lower.
(c) Place the left leg electrode posteriorly over the lower back.

Rule 2: To determine the effect of more marked clockwise rotation of the heart around its long axis, when it has a vertical position with a qR pattern in the left leg lead and an upward T wave:

(a) Place the right arm electrode posteriorly on the right suprascapular region.
(b) Place the left arm electrode anteriorly over the left clavicle.
(c) Place the left leg electrode to the right. (We have previously shown that left leg potentials are similar to those from the left anterior abdominal wall (8), so that the electrode would be moved to the right lower abdominal wall, the right flank or, in extreme cases, to the right lower back.

Rule 3: To determine the effect of less marked clockwise rotation of a vertical heart around its long axis, place the right arm electrode anteriorly, the left arm electrode posteriorly and the left leg electrode to the left.

Rule 2 also holds for a horizontal heart to determine the effect of less marked counter-clockwise rotation of the heart around its long axis; and rule 3 also holds to determine the effect of more marked counter-clockwise rotation of a horizontal heart around its long axis.

Our results in 4 typical cases with vertical hearts are illustrated in figures 8 and 9. In order to simplify the discussion we shall show only the effects of moving the left leg electrode. Figures 8a and b are from the same patients shown in figures 7 and 6, respectively. Patient shown in figure 7 had chronic pulmonary disease. Person shown in figure 6 was normal. Notice how unipolar leads from the right lower back in figures 8a and b have downward T waves.

Figure 9a is the record of a 38 year old woman with extensive pulmonary tuberculosis and a right thoracoplasty. Her heart was almost completely drawn into the right thoracic cage. In the extremity leads, a downward T is present in the left leg lead and leads II and III. However, unipolar leads taken from the left flank and back showed an upward T wave. In this case we have also shown the effect that moving the left leg electrode would have on the standard leads. In figure 9b are shown the special standard leads which were obtained with the left leg electrode placed on the left flank rather than on the left leg. Notice how the T waves of leads II and III have become upright. Figure 9c is from the same patient shown in figure 3c. When the left leg electrode is moved to the left flank or left lower back, T becomes upright.

T wave changes in horizontal hearts: Just as rotation of a vertical heart causes

the T waves of the left leg lead and leads II and III to become downward, marked counter-clockwise rotation of a horizontal heart can cause the T waves of the left arm lead and lead I to become downward, even if the heart is normal in size. This fact has not been appreciated because *it is extremely rare for a normal* horizontal heart to be sufficiently rotated in a counter-clockwise direction around its long axis to cause this, although one of our normal cases presented this finding, and similar cases have been reported in the literature.

Furthermore, deep inspiration in the case of a horizontal heart with a downward T often causes the T of the left arm lead and lead I to become upright (13). Finally, upward and downward T waves can be found in the region

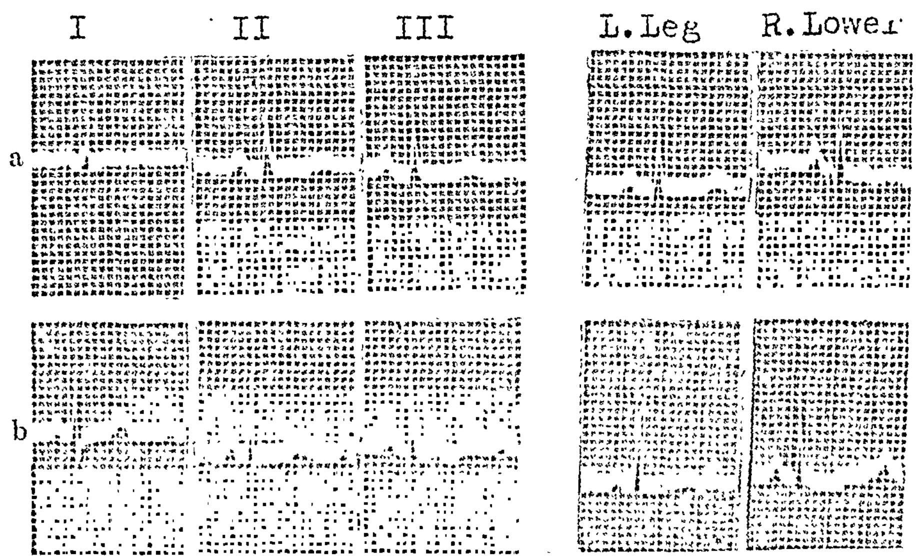


FIG. 8. The effect of moving the left leg electrode to the right in cases with vertical hearts and upright T waves in the left leg lead.
L. Leg: The left leg lead.
R. Lower: Unipolar leads obtained from the right lower back.
a. The same patient as figure 7.
b. The same patient as figure 6.

of the left arm lead (14), using the rules described above. Table 1 shows the incidence of downward T waves in our series. However, rotation of the heart is not the only factor, in the absence of myocardial damage, which can cause the T waves to point downward, either in the horizontal or vertical heart. Such other factors have been described elsewhere (8, 14).

P wave changes: In 1935, Winternitz (15) described a P wave pattern which he considered specific for the pulmonic heart. This consisted of a low P_1. $P_{2,3}$ on the other hand, were high and peaked and often reached an amplitude of 3 or 4 mm., but the base of the P waves had a normal width, not exceeding 0.1 second. This has been questioned by many who feel that the changes are due to rotation of the heart or displacement of the mediastinum (7).

We feel that a combination of forward rotation of the apex and clockwise rotation of a vertical heart around its long axis causes the P waves to appear larger in the left leg lead and leads II and III in addition to causing changes in

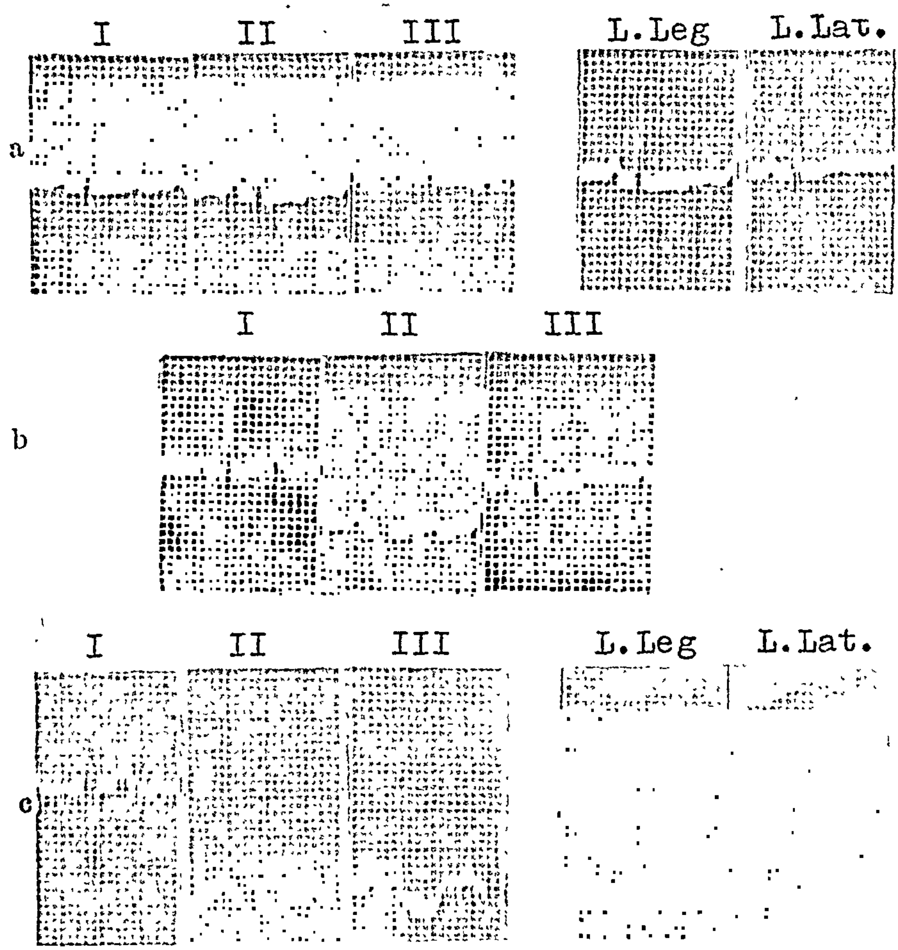


Fig. 9. The effect of moving the left leg electrode to the left in cases with vertical hearts and downward T waves in the left leg lead.

L. Leg: The left leg lead.

L. Lat.: Unipolar leads obtained from the left flank.

a. Case of chronic pulmonary tuberculosis. J. P., female, 38. The patient had a right thoracoplasty and practically the entire heart was drawn into the right chest.

b. The same patient. These standard leads were taken with the left leg electrode on the left flank instead of the left leg. Notice how T2, 3 became upright as a result of shifting the electrode.

c. The same patient as figure 5c.

the QRS and T. Notice the increased amplitude of the P waves in the left leg lead and leads II and III caused by inspiration (figures 6 and 7). A similar change is seen when the left leg electrode was moved to the right lower back (figures 8a and b.). When, as in figure 9a, the left leg electrode was moved to the left, P became smaller.

However, changes in the P wave, due to auricular hypertrophy, do occur. Although our observations of such P wave changes have been limited, we believe that changes in the width of P, in addition to changes in amplitude, are important. On the basis of preliminary observations, we feel that, if P has a width of 0.12 second or more and an amplitude of 3 mm. or more in a standard lead, auricular hypertrophy is present. We further do not believe that a diagnosis of right or left auricular hypertrophy can be made by the presence of the P wave changes in any combination of standard or unipolar extremity leads, because such P wave patterns vary with the position of the heart just as the QRS does. In many of our cases of chronic pulmonary disease we noted large biphasic P waves in precordial leads V_1 and V_2. However, a small biphasic P wave can be observed normally in these leads.

DISCUSSION

Correlation of the electrocardiogram with the radiological position of the heart is not a new idea. Master, for example, published a monograph (21) correlating the electrocardiogram and X-ray configuration of the heart. Gardberg and Ashman (18) more recently have shown that the electrocardiogram can be anticipated by study of the X-ray appearance, and Wilson (17) has already developed a system of describing the electrocardiogram on the basis of the position of the heart.

However, radiological correlation of electrocardiographic patterns is difficult. Although the vertical and horizontal heart can be observed radiologically, at present there is no accurate way of measuring radiologically the degree of rotation of the heart around its long axis or of measuring radiologically forward or backward rotation of the apex. We, however, have begun to study rotation of the apex around the transverse axis of the heart by means of lateral X-ray views with the patient in a recumbent position, in different phases of respiration, and on standing. This lack of knowledge, however, does not invalidate our results. Rather it should serve as a stimulus to further study of the radiological characteristics of the rotated heart. This has probably been the reason why radiological and electrocardiographic correlations of the effect of such factors as pneumothorax, thoracoplasty, etc. have not proved too successful.

The value of an approach, such as ours, can be seen when cases of chronic pulmonary disease are studied over long periods of time, because such findings as left axis deviation changing to right axis deviation, or the development of downward T waves can easily be explained by changes in the position of the heart which occur, although we do not deny that altered cardiovascular dynamics and hypertrophy and even dilatation of the right ventricle can and do occur in the course of the disease process.

CONCLUSIONS

1. The electrocardiographs patterns found in standard leads in cases of chronic pulmonary disease can be explained in terms of the position of the heart, if the basic unipolar patterns of leads from the surface of the right ventricle and from

the surface of the left ventricle are known. In the normal heart or in the heart with moderate right ventricular hypertrophy, the basic right ventricular pattern consists of an rS deflection and the basic left ventricular pattern consists of a qR deflection. The basic pattern from the interior of the heart consists of a QS wave or an rS deflection. The basic pattern from the back of the heart consists of a QR deflection and a downward T.

2. When the heart is vertical the left ventricular pattern and the left leg lead are similar. Since lead III resembles the left leg lead, a qR deflection is found in lead III. When the heart is in such a position, the right and left arms tend to face the interior of the heart and record a Q wave or an rS deflection. Lead I is similar to the left arm lead and an rS deflection is also found in lead I. This pattern is generally described as right axis deviation. It occurs in the normal vertical heart and in a vertical heart which is the seat of moderate right ventricular hypertrophy or of left ventricular hypertrophy.

3. When the apex of a vertical heart is rotated backward, the right ventricle tends to face the left leg and the left leg lead and lead III record an rS deflection instead of a qR deflection. Similarly the right and left arms face the back of the heart and record a QR deflection. In the standard leads this may cause the three standard leads to point downward or lead II to resemble lead I instead of lead III. There is no description of this pattern in terms of axis deviation.

4. When the right ventricle is markedly hypertrophied the basic right ventricular precordial lead changes and consists of a high R wave. If the heart lies vertically this pattern will not be transmitted to the standard leads, but if the apex of such a heart is displaced backward, the right ventricular pattern is projected to the left leg lead and lead III. High R waves appear, but there will be noted the absence of Q waves.

5. When the heart is horizontal the left ventricular pattern, the left arm lead and lead I are similar and consist of a qR deflection. The right ventricular pattern, the left leg lead and lead III are also similar and consist of an rS deflection. This pattern is ordinarily called left axis deviation. If the pattern over the right ventricle has the signs of right ventricular hypertrophy, namely a high R, the left leg lead and lead III will record this, because the heart is horizontal, and left axis deviation will not appear. When the apex of a horizontal heart is displaced backward, lead II tends to resemble lead III instead of lead I.

6. When the vertical heart has forward rotation of the apex and clockwise rotation of the heart around its long axis, the T waves in the left leg lead and lead III become downward. Inspiration or standing can cause this to occur.

7. Similarly a horizontal heart with marked counter-clockwise rotation around its long axis may have downward T waves in the left arm lead and lead I. Inspiration may cause these T waves to become upright.

8. These are only a few of the many positions that the heart can occupy.

9. P waves, 3 mm. or higher are often noted in cases of chronic pulmonary disease. These are also usually due to rotation of a vertical heart. When changes in the P wave due to auricular hypertrophy appear, the base of the P widens to 0.12 second. With auricular hypertrophy, large biphasic P waves may also appear precordial leads V_1 and V_2.

SUMMARY

In this paper we described a method of interpreting standard and unipolar extremity electrocardiograms, and we applied it to normal cases and to cases of chronic pulmonary disease. With our method, the extremity leads are compared to unipolar leads taken taken near the various surfaces of the right and left ventricles. Thus, if lead I and the left-arm lead are similar to a left ventricular lead, it indicates that the position of the heart is such that the left ventricle faces the left arm. The heart is therefore horizontal. However, if lead III and the left-leg lead are similar to a left ventricular lead, it indicates that the left ventricle faces the left leg. The heart is therefore vertical.

Rotation of the heart around its antero-posterior axis, around its long axis and around its transverse axis can be studied in this way. Furthermore, many of the T-wave changes which are often seen can be also explained by this method.

We also showed that the unipolar leads near the surfaces of the heart do not necessarily change with right ventricular hypertrophy. However, right ventricular hypertrophy occasionally produces a characteristic pattern in the right ventricular lead.

Thus, in any case, variations in the standard and unipolar extremity leads are due to:

1. Variations in the basic electrocardiographic patterns in unipolar leads near the heart, and

2. Variations in the position of the heart.

SUMARIO

En este trabajo descríbese un método para interpretar los electrocardiogramas de la punta, tanto habituales como unipolares, que se aplicó en casos tanto normales como de enfermedad pulmonar crónica. Con este método las derivaciones de la punta se comparan con las unipolares obtenidas cerca de las varias superficies de los ventrículos derecho e izquierdo. Por ejemplo, si la derivación I y la del brazo izquierdo son semejantes a la del ventrículo izquierdo, esto indica que la posición del corazón es tal que el ventrículo izquierdo da frente al brazo izquierdo y el corazón es por lo tanto horizontal. Sin embargo si la derivación III y la de la pierna izquierda son semejantes a la del ventrículo izquierdo, esto denota que el ventrículo queda frente a la pierna izquierda, y por lo tanto el corazón es vertical.

En esta forma puede estudiarse la rotación del corazón alrededor de su eje antero-posterior, alrededor de su eje largo y alrededor de su eje transversal. Además pueden también explicarse así muchas de las alteraciones de la onda T que se observan a menudo.

También se demostró que las derivaciones unipolares, cerca de la superficie del corazón, no son alteradas forzosamente por la hipertrofia del ventrículo derecho; pero esta hipertrofia imprime de cuando en cuando un molde característico a la derivación ventricular derecha.

En cualquier caso, las variaciones en las derivaciones de la punta, habituales y unipolares, se deben pues a:

1. Variaciones de los trazos electrocardiográficos básicos en las derivaciones unipolares cerca del corazón, y

2. Variaciones en la posición del corazón.

Appreciation

The authors acknowledge the helpful coöperation of Dr. Max Pinner, Chief, Division of Pulmonary Diseases; Dr. Louis Leiter, Chief, Medical Division; and Dr. George Leiner, Associate Attending Physician, Division of Pulmonary Diseases, Montefiore Hospital; and Dr. Leander H. Shearer, Director of Medicine, Lincoln Hospital.

REFERENCES

(1) Simon, S., and Baum, F.: Electrocardiographic studies in pulmonary tuberculosis, Am. Rev. Tuberc., 1928, *17*, 159.
(2) King, F. W., and Hanson, O. S.: The influence of pulmonary collapse on the electrocardiogram, Am. Rev. Tuberc., 1930, *22*, 310.
(3) Longe, H. J.: Electrocardiogram in tuberculous patients, Am. Rev. Tuberc., 1942, *45*, 528.
(4) Master, A. M.: The electrocardiographic changes in pneumothorax in which the heart has been rotated, Am. Heart J., 1928, *3*, 4.
(5) Anderson, A. R.: Electrocardiographic studies in artificial pneumothorax and thoracoplasty, Am. Rev. Tuberc., 1929, *20*, 728.
(6) Ackerman, L. V., and Kasuga, K.: Chronic cor pulmonale: Its relation to pulmonary tuberculosis, Am. Rev. Tuberc., 1941, *43*, 11.
(7) Fox, T. T., and Kremer, H. S.: The heart in pulmonary tuberculosis: Studies of the auricular complex, Am. Rev. Tuberc., 1943, *47*, 135.
(8) Goldberger, Emanuel: An interpretation of axis deviation and ventricular hypertrophy, Am. Heart J., 1944, *28*, 621.
(9) Goldberger, Emanuel: A simple electrocardiographic electrode of zero potential and a technic of obtaining augmented unipolar extremity leads, Am. Heart J., 1942, *23*, 483.
(10) Goldberger, E., and Schwartz, S. P.: Electrocardiograms in which the main ventricular deflections are directed downward in the standard leads, Am. Heart J., 1945, *29*, 62.
(11) Schwartz, S. P., and Marcus, H.: The electrocardiogram in pulmonary tuberculosis. I. The clinical significance of concordant inverted initial ventricular deflections in patients with chronic pulmonary tuberculosis, Am. Rev. Tuberc., 1942, *46*, 35.
(12) Goldberger, Emanuel: The basic electrocardiographic patterns of bundle branch block, J. Lab. & Clin. Med., 1945, *30*, 213.
(13) Goldberger, Emanuel: The effect of amyl nitrite on the downward T waves of the electrocardiogram, Am. Heart J., in press.
(14) Goldberger, Emanuel: The effect of respiration on the downward T wave of the electrocardiogram and an interpretation of so-called ventricular strain, to be published.
(15) Winternitz, M.: Zur Pathologie des menschlichen Vorhof elektrokardiogramms, Med. Klin., 1935, *31*, 1575.
(16) Goldberger, Emanuel: The aVl, aVr and aVf leads, Am. Heart J., 1942, *24*, 378.
(17) Wilson, F. N., *et al.*: The precordial electrocardiogram, Am. Heart J., 1944, *27*, 19.
(18) Gardberg, M., and Ashman, R.: The QRS complex of the electrocardiogram, Arch. Int. Med., 1943, *72*, 210.
(19) Wilburne, M., and Langendorf, R.: The significance of the electrocardiogram with prominent S waves in leads I, II and III, J. Lab. & Clin. Med., 1942, *28*, 303.
(20) Goldberger, Emanuel: The differentiation of normal and abnormal Q waves, Am. Heart J., in press.
(21) Master, A. M.: The Electrocardiogram and X-ray Configuration of the Heart, ed. 2, Philadelphia, 1942, Lea and Febiger.

BRONCHIOLAR SPASM AS A CAUSE OF REËXPANSION OF A LUNG FOLLOWING INTRAPLEURAL PNEUMONOLYSIS

OTTO C. BRANTIGAN[1] AND REUBEN HOFFMAN[2]

Reëxpansion of a lung, with consequent loss of pneumothorax, is a potential development following closed intrapleural pneumonolysis. When the potentiality becomes a reality, the patient is faced with either a substitute therapeutic measure that is less desirable or postponement until some more radical measure becomes applicable. Not uncommonly, no other collapse measure is indicated or possible and the patient must fall back on expectant treatment.

Postpneumonolysis reëxpansion of lungs can, in a significant number of cases, be prevented. For therapy to be rational, the underlying cause must be recognized. It is the purpose of this article to review briefly the problem of postpneumonolysis reëxpansion and to call attention to a mechanism that is believed to be among the more common causes.

The etiological factors that can precipitate the postpneumonolysis reëxpansion of a lung are (*1*) excessive cough, (*2*) the presence of an endobronchial lesion that produces a check-valve obstruction and (*3*) the production of a check-valve type of obstruction resulting from bronchiolar spasm.

The mechanism in all three instances is the same: increased intrapulmonic pressure which results in the reëxpansion of the lung. The end-result in all three instances is the same: escape of air through the operative wounds into the subcutaneous tissue resulting in loss of the pneumothorax.

If therapy is to be effective in combating the loss of the pneumothorax, the cause must be determined and the proper measures applied. The administration of refills with increasing frequency and in increased amounts is merely substitutive and, when the cause is not combated, will often do no more than delay the ultimate loss of the pneumothorax. The prevention of the loss of pneumothorax in the presence of increasing intrapulmonic pressure would necessitate the maintenance of an intrapleural pressure great enough to overcome the increasing intrapulmonic pressure. There are three obstacles that would prevent such a procedure from being successful: the patient cannot tolerate the intrapleural pressure that would be necessary, the increased intrapleural pressure would augment the rate of absorption of the intrapleural air and the inability to make the operative wounds air-tight would result in the air being forced into the subcutaneous tissue.

The loss of pneumothorax due to excessive cough is usually a simple problem and the therapy equally simple. It is merely important to remember that cough results in a temporary rise in the intrapulmonic pressure sufficient to force the

[1] Department of Surgery, School of Medicine, University of Maryland, Baltimore, Maryland.

[2] Maryland Tuberculosis Sanatorium (Colored Branch), Henryton, Maryland.

intrapleural air into the subcutaneous tissue. Adequate postoperative sedation and proper spacing of refills is all that is necessary.

There is a circumstance, however, when continued cough must be treated by something more than sedation. Ordinarily, the cough initiated by the operative procedure will subside within a short time. Cough that persists unduly long after operation (or if marked before operation) should be suspected as being caused by an endobronchial lesion and bronchoscopic examination should be performed.

The frequent cough may interfere with the maintenance of an optmum pneumothorax even after the operative wounds have healed by producing periodic episodes of increased intrapulmonic pressure with a consequent rise in the rate of absorption of the intrapleural air.

The postoperative loss of pneumothorax due to the presence of an endobronchial lesion that creates a check-valve obstruction has been described (1). Under this circumstance the lung is subjected to an increasing intrapulmonic pressure resulting in a rapid reëxpansion of the lung. Pneumothorax refills, regardless of their frequency or size, fail to prevent reëxpansion and the lung is finally apposed to the chest wall under positive pressure. Failure to reinstitute the pneumothorax, soon after reëxpansion has occurred, is due to the increased intrapulmonic pressure and not to pleural symphysis.

It has been observed that some patients will experience reëxpansion of the lung after complete severance of adhesions by the closed intrapleural route when excessive cough is obviously not a factor and where postoperative bronchoscopy fails to reveal any cause for the reëxpansion. Since the reëxpansion in these cases usually involves the whole lung, the presence of an endobronchial lesion (after normal bronchoscopic findings) cannot be entertained as the cause. To explain such a reëxpansion on the basis of an endobronchial obstruction would require a check-valve mechanism in the main bronchus or at the several orifices of the branch bronchi. To postulate the presence of check-valve obstruction in the several branch bronchi outside the visual field of the bronchoscopist (as justification for normal bronchoscopic findings) does not merit serious consideration.

To explain the reëxpansion of a lung under the circumstance when excessive cough and endobronchial disease are not the causes, we have postulated that the cause is spasm of the terminal bronchioles (or alveolar ducts) and that this spasm creates a check-valve type of obstruction with resultant increased intrapleural pressure.

That bronchiolar spasm can bring about this sequence of events finds some support in the fact that this mechanism is encountered in asthma. Further suggestive evidence was obtained when the administration of a drug that overcomes bronchiolar spasm prevented reëxpansion of the lung (when the use of the drug was the only procedure employed). As increasing experience with this condition was obtained, it became obvious that the lung had a characteristic appearance and could be readily recognized at time of thoracoscopic examination and by the characteristic behavior both operatively and postoperatively.

At thoracoscopic examination the lung which is kept partly inflated by the bronchiolar spasm has a voluminous appearance. The pulmonary edges are rounded as is the site of the pulmonary origin of the adhesion(s). During operation the lung has a tendency to reëxpand and, in some instances, reëxpands sufficiently to interfere with the operative procedure. Even when all adhesions have been severed, the degree of collapse obtained is disappointing and never as much as would have been expected. In some instances the severance of the adhesions does not increase the degree of collapse at all. Postoperatively, this type of lung shows a definite (and sometimes marked) tendency to reëxpand with a concomitant amount of subcutaneous emphysema. Reëxpansion occur often in spite of frequent refills.

The appearance, operative and postoperative behavior of the voluminous lung are in striking contrast to the appearance and behavior of the lung in which bronchiolar spasm does not exist. Under this circumstance the pulmonary edges are sharp and the pulmonary attachment of the adhesion(s) is thin and sharp. In addition, patchy areas of atelectasis are visible. At operation there is no tendency to reëxpand and when the adhesions have been severed, the lung promptly deflates Postoperatively the lung (according to X-ray examination) remains well collapsed, there is very little or no subcutaneous emphysema, immediate postoperative refills are hardly ever necessary and subsequent refill schedules are usually lengthened. Subsequently, the uninvolved lung reëxpands in whole or part with the diseased lobe(s) remaining selectively collapsed.

The postoperative management of the lung subjected to bronchiolar spasm is relief of the spasm until the tendency to reëxpand is overcome. Formerly, this type of lung was diagnosed at time of operation and reëxpansion of the lung predicted, but treatment was withheld until reëxpansion of the lung had actually begun. It was found that 0.5 cc. of adrenalin (1:10,000) and 25 mg. of ephedrine sulfate given intramuscularly every four hours for twenty-four to forty-eight hours overcame the spasm. At present, if this condition is diagnosed at operation, treatment is begun immediately upon completion of the pneumonolysis. In place of adrenalin and ephedrine, 0.5 cc. of adrenalin (1:500) in oil is used. It is given intramuscularly immediately after operation and every four hours for twenty-four to forty-eight hours. This usually suffices to overcome the spasm. If there is evidence that the spasm persists, the medication is reinstituted for an additional twenty-four hours.

Response to therapy has been uniformly good. No untoward effect from the use of adrenalin has been noted. An occasional patient will complain of being nervous. Patients frequently comment that the act of expectoration becomes easier after the administration of the drug.

COMMENT

There are many questions associated with bronchiolar spasm that need to be answered. However, we feel that it is not fruitful to indulge in mere speculation and we attempt no exposition of the problem. Our purpose is merely to call attention to the fact that the condition exists. We feel certain that the sequence

of events we have described has been observed by those who have had any appreciable experience with closed intrapleural pneumonolysis.

For the present it is sufficient that the condition of bronchiolar spasm can be recognized at operation and reëxpansion prevented by the appropriate use of adrenalin. This condition is worthy of attention, since, in our experience, it is one of the more common causes for postoperative reëxpansion of a lung.

SUMMARY

Attention is called to the fact that reëxpansion of a lung, following successful severance of adhesions by way of the closed intrapleural route, may occur in the absence of demonstrable endobronchial disease and in the absence of excessive cough.

It is postulated that such reëxpansion is due to bronchiolar spasm when excessive cough and endobronchial disease can be ruled out as causes.

The "voluminous" appearance of the lung, its tendency to reëxpand during operation and after operation in spite of frequent refills are characteristics that sharply differentiate this condition from the usual uncomplicated operative course and postoperative management of the lung that is free from endobronchial disease and not subjected to bronchiolar spasm.

Treatment of the bronchiolar spasm with adrenalin has given uniformly good results and the tendency to reëxpand is sharply diminished and frequntly abolished.

SUMARIO

Llámase la atención sobre el hecho de que la reexpansión de un pulmón, después de resecarse las adherencias por vía intrapleural cerrada, puede tener lugar, aún sin haber enfermedad endobronquial observable y tos excesiva.

Postúlase que dicha reexpansión se debe a espasmo bronquiolar cuando pueden excluirse como causas la tos excesiva y la afección endobronquial.

El aspecto "voluminoso" del pulmón, su tendencia a reexpandirse durante la operación y después a pesar de las frecuentes, reinsuflaciones, constituyen características que diferencian totalmente dicho estado de la habitual evolución operatoria sin complicaciones y el tratamiento postoperatorio del pulmón que se halla exento de afección endobronquial y no experimenta espasmos invariablemente buenos y tiende a atenuar y frecuentemente a hacer desaparecer la tendencia a la reexpansión.

REFERENCE

(1) Brantigan, Otto C., Hoffman, Reuben, and Proctor, Donald F.: Endobronchial tuberculosis, Am. Rev. Tuberc., 1942, *45*, 477.

RESPIRATORY MALFORMATIONS[1]

Types, Causes and Significance

A Preliminary Report

HOVEY JORDAN

Sometime ago, in connection with a detailed study of two new human cases showing the same type of anomalous development of respiratory tissue (14) (figures 1, 2), and a review of the literature on the subject, a comprehensive morphological classification of the various types of respiratory malformations (anomalies) was published (1).

Structural anomalies of the respiratory system and of respiratory tissue resulting from abnormal development may, in general, be grouped, for the purposes of this preliminary report, into two inclusive classes: first, those which are connected to or are a part of the respiratory system and, second, those which are not connected to any part of this system. The first group includes such types as abnormal lobes or fissures of the lung itself, and agenesis of a lung (2, 3). The second group, on the other hand, not only have no morphological connection to the definitive respiratory system, but often seem to arise independently of this system and of its anlage[2], as will be described below.

With respect to anomalies of this second group, that is, anomalous respiratory tissue which is not connected to any part of the respiratory system, it should be noted that there are two subdivisions (IH_1 and IH_2) in the more extensive classification (1). One of these, IH_1, includes anomalous lobes which are pedunculated to some nonrespiratory organ or structure, such as the wall of the posterior mediastinum, diaphragm, body wall or even to the alimentary tract. It is to this group that the 2 new cases studied in our laboratory belong (figures 1 and 2).

Both of these anomalous lobes were essentially identical in morphology and relations, as well as in the structure and site of attachment of their pedicles. In each case the lobe was located in the left pleural cavity just above an intact diaphragm and posterior (dorsal) to the lower lobe of the left lung. The posterior surface of these anomalous lobes were convex (figure 2) and fitted into the concavity of the posterior thoracic wall. The anterior surfaces were flat (figure 1) and rested upon the posterior aspect of the lung. Both of these lobes were attached by a pedicle to the pleura of the left wall of the posterior mediastinum where this wall joins the superior surface of the diaphragm and the posterior body wall (figures 1 and 2). In each case a reflection of parietal pleura which formed the wall and stroma of the pedicle also continued around the anomalous lobe to enclose it as a pleural (serous) covering. Neither of the pedicles con-

[1] From the Laboratory of Histology-Embryology, Department of Anatomy, College of Medicine, University of Vermont, Burlington, Vermont.

[2] It is planned later to publish a comprehensive and detailed account of the study which has been partially completed.

FIG. 1. (Upper) Case 1. The anomalous lobe, type IH_1, in the thoracic cavity of a full-term stillborn male fetus, showing the pedicle which attaches the abnormal lobe to the pleura of the left wall of the posterior mediastinum where this wall joins the diaphragm and posterior body wall. The pedicle contained blood vessels and nerves but no bronchi. Forceps are clamped onto the edges of the diaphragm.

FIG. 2. (Lower) Case 2. Posterior view of the lungs, diaphragm, pedicle and anomalous lobe, type IH_1, of a male infant. The anomaly rests on a small piece of white paper. Glass tubes are inserted in the esophagus and trachea, which project through the inferior surface of the diaphragm.

tained any bronchi, although there were numerous blood vessels in each one which supplied the tissue of the anomaly. Numerous nerve trunks, and in one case ganglion cells, were also present in the pedicles. Each of these abnormal lobes was free in the left thoracic cavity, except for this pedicular attachment. Both malformations were of about the same size. The anomalous lobe in case 1, a stillborn, full-term, male fetus, was 30 mm. long and 25 mm. wide; while that of case 2, a year old male infant who died of complications following a severe burn, was 8 mm. longer.

Histologically (figures 3 and 4) each anomaly is seen to consist entirely of lung tissue which, however, is somewhat atypical in structure and organization. The bulk of the tissue in each case is made up of alveoli (really pseudo-alveoli) of varying sizes and shapes. Numerous bronchioles which are somewhat variable in structure are present and these are seen in some instances (figures 3 and 4) to lead into the alveoli. Each alveolus in case 1 (figure 3) is lined by a cuboidal epithelium and none of the alveoli were collapsed, even though no air could have reached them. It is also interesting to note that these alveoli contained little or no fluid. The expansion of these pseudo-alveoli, then, would seem to be the result of the pattern of growth of the parent tissue (anlage) of the malformed lobe. In case 2 (figure 4) some of the alveoli are expanded and have the same cuboidal lining as in the first case, although in other regions of the anomaly many of the alveoli appear to be relatively unexpanded and present the picture of much more typical lung tissue. The stroma of each anomaly is composed of areolar connective tissue in which are numerous small blood vessels. All of these vessels appear to be purely nutritive in character and none of them seem to have a position in relation to the alveolar walls which would be expected if they were of respiratory nature.

In all, about 50 such cases have been described. On the basis of their morphology and relations (figures 1 and 2), as well as on their histological picture (figures 3 and 4), anomalous tissue of this type, IH_1, seems, in general, to constitute a definite anatomical entity; although in some instances (22, 24) cases have been reported which are intermediate between this group and the second division in the more extensive classification (I), that is type IH_2, below. These intermediate cases might, on the basis of certain characteristics, be classed in either group. Anomalies of type IH_1, principally, have often been included in a general and miscellaneous group, as far as origin and structure are concerned, which are called collectively "inferior accessory lobes," Schaffner (11) and Soper (8a), or "lower accessory lungs," Davies and Gunz (12). None of these anomalous lobes (IH_1), however, are connected to the respiratory system and, therefore, they are not true accessory lung lobes. They are, rather, supernumerary, anomalous lobes or masses of atypical and nonfunctional respiratory tissue.

One great significance of these cases is that they serve as a good basis for a reëxamination and extension of our ideas concerning the origin and clinical significance of respiratory malformations and this principle applies, also, to the second subdivision, IH_2. These, likewise, are a more or less definite anatomical entity, although they are closely related in method of origin and essential sig-

FIG. 3 (Upper) Case 1 A section of the anomalous lobe showing the pleural covering, stroma and pseudo-bronchi leading into pseudo-alveoli. These alveoli were all expanded, contained no fluid and were lined by a cuboidal epithelium.

FIG 4. (Lower) Case 2 A section of the anomalous lobe, showing essentially the same features as that of case 1 In certain regions this anomaly had differentiated into somewhat more typical lung tissue than that of case 1, although pseudo-alveoli lined by cuboidal epithelium are present here as seen in this section.

nificance as well as in structure and relations in some instances to type IH_1, as noted above. They would be included generally and under more or less common usage in that nonspecific and miscellaneous group of anomalous structures of respiratory nature which, regardless of origin and anatomical relations, are frequently called bronchogenic, respiratory or pulmonary cysts (26, 39). This second group differs from the first chiefly in the facts that the anomalous respiratory tissue is not pedunculated to but rather included in the wall of some nonrespiratory structure, usually but not always in the wall of the esophagus, gut or mediastinum (from which it may protrude in varying degree, thus in some cases resembling type IH_1) and, further, that it is more or less cystic in nature. Somewhat fewer cases of this type of structural anomaly have been described than of type IH_1, in all about 30 have been reviewed. One unusual case was described to the author by Doctor Wolbach with permission to publish (4), in which a cyst of respiratory tissue (type IH_2) was found in the subcutaneous tissue of the human posterior body wall in the midthoracic region. An anomaly in this same category has also been reported to the author by Doctor Farber (32) with permission to publish. It presumably should be classed as type IH_2. The description follows: "In an infant eleven months of age a cystic mass in the midline at the level of the upper sternum had been noted since birth, a small dimple was present on the skin, but no connection could be found between the dimple and the tumor below. The mass, on surgical exploration, was found to be a thin walled cyst 1.2 cm. in diameter connected to the dimple in the skin by a fibrous cord. There was no connection with any of the structures in the bed of the cyst. There is no cartilage present but the structure appears to be a respiratory tube." So far as known these are the only cases of subcutaneous respiratory malformations ever to have been reported in man. Several cases, however, of such anomalies have been described in animals (5).

The question of origin of respiratory malformations, both as to the site and method of their development, has long been a matter of uncertainty and difference of opinion. Our study has led to certain conclusions, some of which have already been published (14), and others of which may be mentioned here in brief form. Since abnormal respiratory structures vary so greatly in their anatomy and relations, they cannot well be considered collectively in any adequate theory or explanation of origin. They must, apparently, be broken down into at least the two general classes mentioned in this paper, that is, those which are connected to some part of the respiratory system and those which are not connected to any part of this system. The embryological origin of those anomalies which are connected to the respiratory system is, obviously, from the anlage of that system and probably from a variety of causes. We may omit further consideration of this group here and turn to the second group, those respiratory malformations which are not connected to the respiratory system. The evidence of our 2 cases and a detailed examination of the literature indicates that most of these anomalies arise from an evagination of the early embryonic gut which is independent of the respiratory anlage and of the laryngo-tracheal groove. This seems to be true both for types IH_1 and IH_2. The facts that the cystic type

(IH_2) is most frequently incorporated in the wall of the esophagus (18) and may even occur in the subcutaneous tissue of the posterior body wall (4), or in that of the anterior body wall (32) and that some of the pedunculated anomalies (IH_1) are distal expansions of a tubular evagination from the stomach (6) or gut and possess an epithelium which is continuous with that of the gut, are more difficult to explain on any other basis.

In amplification of this conclusion it may be said that many investigators have considered anomalous respiratory structures generally, including types IH_1 and IH_2, to be derived from some part of the respiratory anlage by *Abschnürung* (constriction), for example (11, 13, 17, 20). Davies and Gunz (12) have, however, discarded this theory as being inadequate to explain anomalies of respiratory tissue belonging to type IH_1, and with that conclusion the present author agrees. Other investigators, as a second theory of origin, have regarded many respiratory malformations, including type IH_1 as the result of a drawing away of certain cells from the respiratory anlage or from the borders of the laryngo-tracheal groove to an abnormal location during development. Davies and Gunz (12) use the word sequestered or outlying for the misplaced embryonic tissue involved in this process. The fundamental idea of this drawing away or sequestering of cells from an organ anlage was previously suggested, not only for structural respiratory anomalies but, by implication, for those of any system by Zenker (35) and by Ribbert (15) and is implied in Ribbert's title, *Zur Kentniss der Tractions-Divertikel des Oesophagus.* It has, moreover, been applied to the respiratory system by Cockayne and Gladstone (21) and others. Corner (37) has studied the region of the laryngo-tracheal groove in an embryo of 10 somites and Gruenwald (7b) comments on the rapid growth of the tissue of this region as compared with that of the gut proper. This fact may be significant in considering the possible validity of the traction band (sequestration) theory as an adequate explanation of the origin of respiratory malformations. Both of the above theories presuppose the origin of anomalous respiratory structures to be from embryonic tissue which is derived from the respiratory anlage in some mechanical manner, that is, from embryonic tissue which has already assumed a respiratory nature at or adjacent to the site of the normal anlage of this system.

On the other hand, the third possibility, which has been more or less clearly expressed by some authors mentioned below, but which is frequently not clearly differentiated from the traction band or sequestration theory above, seems to be most generally applicable in explaining the origin of those anomalies of respiratory tissue which are not connected to the respiratory system (types IH_1 and IH_2). This possibility, as mentioned above, is that many of these anomalies develop from an abnormal and supernumerary evagination of the early embryonic gut which is independent of the laryngo-tracheal groove region and of the respiratory anlage itself. The tissue of this evagination, therefore, would not be expected to possess any respiratory potentialities under normal developmental processes (Jordan (14)). The explanation of this anomalous evagination may well be an improperly localized and imperfect histological differentiation in the

gut entoderm of the very young embryo which occurs even before the formation of the respiratory anlage as a definite primordium. This is a stage which is earlier than those usually considered in attempting to explain respiratory malformations. Such an hypothesis is not inconsistent with the ideas of Eppinger (36), Rouvillois and Delater (31), Bert and Fischer (34) and Eppinger and Schauenstein (19). This hypothesis makes it unnecessary to attempt the difficult and doubtful explanation of retroperitoneal attachment following constriction of a bronchial bud, of growth or migrations within the narrow limits of the posterior mediastinum and of other problematical spatial relationships, as well as of the atypical blood and nerve supply which the constriction theory requires. This independent evagination hypothesis, it should also be noted, seems to have the advantage over the traction-band or sequestration theory of explaining some of these anomalous structures, particularly those in the body wall (4, 5, 32) and those attached to or included within the wall of the alimentary tract (18, 19), better than any other theory of origin. It does not involve the necessity of explaining difficult and theoretical mediastinal and other anatomical relations, and the translocation of embryonic respiratory tissue necessitated by the traction-band theory. It is, moreover, not inconsistent with the preponderantly left-sided occurrence of the anomalies of group IH_1. Neither is it necessary with this theory to assume an arrested development of the anomalous tissue beyond the probable effect of one developing tissue upon tissues adjacent to it and beyond the possible effects of physiological gradients, Child (25), as is done by Davies and Gunz (12), because the fundamental concept in this third theory is that these anomalous structures arise from cells in the very early embryonic gut which are abnormal from the beginning, both in position and in possessing respiratory rather than digestive system potentialities, that is, that each of these malformations is a developmental anomaly which starts from an atypical evagination of the gut entoderm in the very young embryo and that this evagination possesses within its component cells the determinants for the ultimate size as well as for the degree and type of abnormal pseudo-respiratory differentiation which the resultant anomaly attains. The study of a considerable number of anomalies of types IH_1 and IH_2 has led to the conclusion that, in general, they reach the limit of their growth in size and of their histological differentiation into pseudo-respiratory tissue of one type or another either prenatally or early in postnatal life and that they do not change materially from this condition in later life. In this connection it is interesting to note that Needham (38) believes the factor for histological differentiation to be relatively independent of that for growth, that is, that growth and differentiation occur independently of each other. An essentially similar conclusion has been reached as a result of the study of the 2 new cases described in this paper. Numerous cases are reported where these malformations, having essentially the same structure as that described for those which are found at autopsy in infants and children, have been found at autopsy in middle-aged or elderly people, for example, Stilling (22), in a man 45 years old; Springer (23), in a 49 year old woman; Robsmann (24), in a 56 year old man.

The detailed considerations which have led to the above conclusions as to the origin and morphological history of these anomalies are too lengthy for this report, but it is planned to present them at a later date. It should, however, be emphasized here that there is no intention of minimizing the importance of the laryngo-tracheal groove region of the embryo, nor indeed, of flatly denying the possibility of origin of some of these anomalous respiratory structures from that region. It will even be suggested in the subsequent article that the same type of anomaly may arise by different methods and from different sites in occasional instances. This principle may apply to the types of anomalies (IH_1 and IH_2) which we are now considering.

On the question of origin of these anomalies it may, therefore, be said in summary: First, that there seems to be some agreement at present (12) on the inadequacy of the constriction theory to explain the origin of all anomalous respiratory structures, particularly the majority of types IH_1 and IH_2. Second, that the traction-band or sequestration theory (12, 15, 35) may, possibly, explain some of these anomalies although it necessitates a difficult and somewhat doubtful explanation of the translocation of cells of the respiratory anlage to abnormal positions on the basis of differential or abnormal growth, mechanical factors and spatial relationships. (Both of the two above theories are identical, it should be noted, in that they presuppose the origin of the anomalous tissue to be from cells which are respiratory from the beginning, that is, from cells of the respiratory anlage or of its immediate environs. The difference between these two theories, then, is largely the concept of the age of the embryo at which the anlage of the anomaly starts to develop and, therefore, of the mechanical means by which the definitive anomalous structure is formed.) Third, that the theory of independent evagination of the anlage of the anomaly from the very early embryonic gut, because of faulty differentiation of this gut into respiratory instead of into gut tissue at the site of the evagination, seems to be the most likely explanation for the origin of the majority of the anomalies of types IH_1 and IH_2. This seems to be true for most of those anomalous lobes which are pedunculated to nonrespiratory organs or structures (figures 1 to 4), those similar ones which remain attached by a pedicle to the gut (19), as well as for the more or less cystic types (IH_2) which develop and remain within the wall of the gut or protrude somewhat therefrom, for example, esophageal cysts (18) and, also, probably for "respiratory" cysts lodged in the body wall (4, 32), and particularly when these are in the lower trunk region (5). Fourth, that these anomalous structures are developmental abnormalities both grossly and microscopically, and not true neoplasms as has often been implied.

According to recent studies of autopsy material (7a), structural abnormalities of the respiratory system and of respiratory tissue of one type or another occur in about one out of every hundred cases. On the other hand, anomalous lobes at or near the base of the lungs, irrespective of their connection to the lung, that is, the inclusive and nonspecific group called "inferior accessory lobes," are thought to occur much more frequently as judged by a study of X-ray plates (11). In this survey (11) such anomalous lobes are reported to occur in about

46 per cent of the persons examined, that is, one such anomaly was formed in each 2.2 cases, approximately. This is an unusually high percentage, so high in fact, when compared with autopsy findings (7a), that it appears necessary to discount the figures somewhat. This discrepancy may be due to the difficulty of reading X-ray plates and to individual differences in interpretation. Gräberger (8b) has considered the diagnostic significance and interpretation of basal paramedian shadows which, in general, are caused by these "inferior accessory lobes." Soper (8a) has studied the azygos lobe as revealed by X-ray plates and reports that slightly less than 1 per cent of 1,600 men showed an X-ray shadow of this lobe. This, of course, is a shadow near the apex of the lung, as contrasted with the basal shadow cast by the so-called "inferior accessory lobes." The figures of percentage occurrence of structural respiratory anomalies given by Gruenwald (7a) and by Soper (8a) are very similar, indicating, say, a possible occurrence of respiratory malformations in about 1 to 2 per cent of the population. This tentative figure is believed to be a fairly good norm, as compared with the higher figure of Schaffner (11). It may, of course, be that the frequency of occurrence of these anomalies varies somewhat with different families, races and localities. It is, moreover, obviously impossible to set an exact and entirely accurate figure.

While an explanation of the origin in some instances and of the frequency of occurrence of respiratory malformations is somewhat problematical and theoretical, their clinical significance is a matter which is eminently practical and one which merits careful attention; not because these anomalies are, *per se*, likely to be the site or cause of disease in disproportionately large numbers, but because it is important, so far as possible, to recognize them as anomalous structures of developmental origin, certain types of which may become diseased and particularly to differentiate them from other definite clinical syndromes.

This study has led to certain conclusions as to the clinical significance of these atypical respiratory structures some of which may be briefly summarized here: Practically no case of disease in an anomaly of type IH_1 (anomalous lobes of respiratory tissue pedunculated to a nonrespiratory organ or structure) was found which was diseased independently of the rest of the body. In fact, very few cases of disease in these rare anomalies have been reported. Humphrey (28) describes a tuberculous process in the centre of an anomaly of this type in a patient who died of tuberculous meningitis and Rouvillois and Delater (31) report tuberculosis in a similar anomalous lobe. Darier (29) mentions a "diphtheritic bronchopneumonia" in the case reported by Hugenin and Sorel (30) and concludes that this disease must have been blood-borne because there was no connection between the tracheobronchial tree and the alveoli of the anomaly. Hugenin and Sorel's title indicates that disease of the anomalous lobe caused death, which seems doubtful. The blood-stream is the only apparent route by which toxins, bacteria or viruses can reach anomalies of this kind and any pathogenic substances must therefore, as Darier concludes, reach them in that way. In one case only did an anomalous lobe of type IH_1 cause clinical signs

and symptoms which led to its diagnosis by X-ray (Rouvillois and Delater (31)). These authors say that in this case the anomaly simulated a tumor of the mediastinum. This anomalous lobe was subsequently removed by surgery. Most anomalous lobes of this particular type (IH_1), then, do not become diseased, give no signs and symptoms and are usually found at autopsy, often in people who have had a long life span.

Respiratory malformations of type IH_2, (anomalous respiratory tissue which is more or less cystic in nature and incorporated in the wall of nonrespiratory organs or structures, or which protrudes from them in a pseudo-pedunculated manner resembling or grading into type IH_1 above), constitute, like IH_1, but a very small percentage of respiratory anomalies *in toto*, and, like those of IH_1, they are not of major clinical significance. They would be included by some investigators, as might also be some of the IH_1 types above, in the general and nonspecific group called "bronchogenic or respiratory cysts."

True bronchogenic cysts, however, which develop from and retain a more or less complete connection to some part of the respiratory system, do have considerable clinical significance (26) in contradistinction to the type IH_2 anomalies. Many of these true bronchogenic or pulmonary cysts not only become diseased, as might be expected because of their connection to the tracheobronchial tree, but have been diagnosed by X-ray and treated surgically or otherwise (Brown and Robbins (26), Tyson (39)).

It is particularly interesting to note that none of the anomalous respiratory structures comprising groups IH_1 and IH_2, above, showed any indication of malignancy. This fact may have some theoretical bearing on the question of cancer. In one of our cases, and in several cases described in the literature, there were connective tissue abnormalities corresponding to similar ones in other parts of the body, but these were not of a malignant nature.

Anomalous accessory lung lobes, including "inferior accessory lobes" and other types, which are merely pedunculated to the lung without any functional (bronchial) connection are apparently no more subject to disease than is the normal lung tissue. Epplen and Jacobson (10) have, however, described a small nonfunctional anomalous lobe, which was pedunculated to the upper left lobe in an old man with hydrothorax, in which the pedicle became twisted. As a result, the blood supply of this lobe was partially shut off and a more or less gangrenous condition resulted.

There are, however, as would be expected, many examples of disease in the functional accessory lobes, including "inferior accessory" and azygos types. Soper (8a) has described pneumonia in the azygos lobe and Mackmull (16) discusses physical signs resembling those of pulmonary tuberculosis which resulted from the addition of this azygos lobe and an anomalous azygos vein "to the right thoracic apex." Disease in these lobes is probably explained by their connection to the bronchial tree and by their pulmonary and bronchial blood supply.

Recently bronchoscopic lipiodol roentgenograms of the tracheobronchial tree have been made use of to diagnose cases of agenesis of a lung (3).

The thorax and the mediastinum in particular, is a region where anatomical relations are a bit difficult to understand, particularly from the developmental point of view, and where diagnosis is sometimes difficult. It should be noted that many authors mention tumors, in this case true neoplasms and not respiratory malformations, of the thorax and mediastinum; for example, Imber (27) describes a tumor of the superior pulmonary sulcus, Kent *et al.* (33) discuss intrathoracic neurogenic tumors and Blades and Dugan (9) have described tuberculoma of the posterior mediastinum. Zingg (40) has described 229 mediastinal dermoids. It is interesting to recall, in this connection, that Rouvillois and Delater (31) said that their anomalous lobe of type IH_1 with a tuberculous process simulated a tumor of the posterior mediastinum.

In other words, the differential diagnosis between anomalous respiratory structures, whether diseased or otherwise, from the true neoplasms and other clinical conditions is a matter of considerable importance and one which may involve anomalies of type IH_1, IH_2, as well as supernumerary lung lobes which are functional or which have no connection to the bronchial tree and true respiratory cysts. Respiratory malformations do not occur in any great percentage of persons and a relatively small proportion of those anomalies which do occur ever become diseased. Most of these malformations do not interfere with normal physiological processes unless they are so extensive, or are so associated with other structural anomalies, as to cause some vital deficiency. They do, however, often cast X-ray shadows which need careful interpretation and they may alter the physical findings in certain cases. The types of structural respiratory anomaly which seem most often to become diseased are those bronchogenic or respiratory cysts which are connected to the tracheobronchial tree and functional anomalous or named accessory lobes of the lung which likewise are connected to this tree. Mackmull (16) quotes a statement of Professor Schaeffer's which is repeated here because it is particularly significant in the consideration and interpretation of the structural respiratory anomalies which we have been considering, as well as of those of any other system. It would seem to be applicable to routine examination and diagnosis: "The adherence to a single, fixed and arbitrary normal is fraught with danger, since with variations come altered size, shape, altered anatomical relations. Morphological variations must necessarily have an important bearing on physical diagnosis, pathology, clinical medicine and surgery."[3]

Perhaps the chief clinical significance of these respiratory anomalies, then, is the fact that, while they are present in relatively few individuals, there is always the possibility of one type or another of them being present in any given case, particularly where thoracic diagnosis is doubtful or obscure. In any differential diagnosis of such cases a knowledge of the specific types of respiratory malformations both as to their location, relations, structure, and relative frequency of

[3] From the Laboratories of the Daniel Baugh Institute of Anatomy, Jefferson Medical College, Philadelphia, Pennsylvania.

occurrence as well as to their likelihood of becoming diseased, of casting X-ray shadows and of altering the physical signs, would seem to be of considerable importance for a correct interpretation.

SUMMARY AND CONCLUSIONS

1. Respiratory malformations (structural anomalies of the respiratory system or of respiratory tissue) occur in about 1 to 2 per cent of persons. Abnormalities of lobes and fissures are most frequent. Agenesis of a lung, anomalous respiratory tissue pedunculated to a nonrespiratory structure (IH_1) and cysts of respiratory tissue within the wall of a nonrespiratory organ or structure (IH_2) are the types which occur least frequently.

2. In explaining the embryological origin of anomalous respiratory structures it is necessary to consider their morphological classification. Malformations of the respiratory system itself are explained by abnormal development of the respiratory anlage. Malformations of types IH_1 and IH_2 are best explained in most cases by assuming their development to be not from the respiratory anlage or its environs, but from an independent evagination of the very early embryonic gut due to faulty histological differentiation.

3. These malformations do not become diseased more frequently than do other somatic tissues and manifest no particular tendency toward malignancy. Functional accessory lobes and respiratory cysts connected to the tracheobronchial tree become diseased most frequently, types IH_1 and IH_2 and nonfunctional lobes least frequently.

4. Each anomaly of type IH_1 and IH_2 possesses individual potentialities for growth and differentiation into pseudo-respiratory tissue which are attained either prenatally or early in postnatal life. These anomalies are not true neoplasms, but developmental abnormalities with the above characteristics.

5. It is important, particularly in thoracic diagnosis, to realize that a respiratory anomaly may be present in any case, that it may alter physical findings and X-ray shadows, and to differentiate these anomalies from other clinical conditions of the thorax and mediastinum. In this diagnosis a knowledge of the various morphological types of respiratory anomalies, of their frequency and site of occurrence and of their tendency to become diseased is of basic importance.

SUMARIO Y CONCLUSIONES

1. Aparentemente en 1 a 2% de las personas existen vicios de formación del aparato respiratorio (anomalías histólogicas del aparato mismo o de los tejidos). Los más frecuentes son anomalías de los lóbulos y grietas, siendo los menos frecuentes la agenesia de un pulmón, tejido respiratorio pediculado a un tejido no respiratorio (IH_1) y quistes de tejido respiratorio dentro de la pared de un órgano o tejido no respiratorio (IH_2).

2. Al explicar la embriogenia de los tejidos respiratorios anómalos hay que considerar su clasificación morfológica. Los vicios de formación del aparato mismo son explicados por el desarrollo anormal del anlaje respiratorio. Los

vicios de formación de los tipos IH_1 y IH_2 se explican mejor en la mayoría de los casos, dando por sentado que se desarrollan, no del anlaje respiratorio o de las cercanías de éste sino de una evaginación independiente del mesogastrio embrionario muy temprano debido a defectuosa diferenciación histológica.

3. Esos vicios de formación no se enferman más frecuentemente que los otros tejidos somáticos y no manifiestan tendencia cancerosa. Los lóbulos accesorios funcionales y los quistes respiratorios unidos al árbol tráqueobronquial son los que se enferman más frecuentemente y los tipos IH_1 y IH_2 menos frecuentemente.

4. Cada anomalía de los tipos IH_1 y IH_2 posee sus propias potencialidades de desarrollo y de diferenciación en tejido seudo-respiratorio, que alcanza bien en la época prenatal o tempranamente en la postnatal. Esas anomalías no son verdaderas neoplasias sino vicios del desarrollo dotados de las características mencionadas.

5. Es importante, en particular en el diagnóstico torácico, comprender que en cualquier caso pueden existir anomalías del aparato respiratorio, que pueden alterar los hallazgos físicos y las sombras roentgenológicas y diferencian esas anomalías de otros estados clínicos del tórax y mediastino. En esta clase de diagnóstico reviste importancia primordial el conocimiento de los varios tipos morfológicos de las anomalías del aparato respiratorio, de su frecuencia y localización y su tendencia a volverse patológicas.

REFERENCES

(1) JORDAN, H.: Anomalies of the human respiratory system: A proposed classification, Am. Rev. Tuberc., 1939, *40*, 517.

(2) HURWITZ, S., AND STEPHENS, B.: Agenesis of the lung: A review of the literature and report of a case, Am. J. M. Sc., 1937, *143*, 81.

(3) FERGUSON, C. F., AND NEUHAUSER, E. B. D.: Congenital absence of the lung (agenesis) and other anomalies of the tracheobronchial tree, Am. J. Roentgenol., 1944, *52*, 459.

(4) WOLBACH, S. B.: Dept. of Pathol., Harvard Medical School: Verbal and written communication and section of the anomaly, 1939–1945.

(5) SJOLTE, I. P., AND CHRISTIANSEEN, M. J.: Zehn Fälle von Nebenlungen bei Tieren, Arch. f. path. Anat., 1938, *302*, 93.

(6) SCHEIDEGGER, S.: Lungenmisbildungen (Beitrage zur Entstehung der Nebenlungen), Frankf. Ztschr. f. Path., 1935–6, *46*, 362.

(7a) GRUENWALD, P.: A survey of congenital anomalies as found in 1131 necropsies, Illinois M. J., 1940, *78*, 293.

(7b) GRUENWALD, P.: A case of atresia of the esophagus combined with tracheolaryngeal fistula in a 9 mm. embryo, and its embryological explanation, Anat. Rec., 1940, *78*, 293.

(8a) SOPER, W. B.: Some clinical aspects of accessory lobes of the human lung, Yale J. Biol. & Med., 1923, *5*, 226.

(8b) GRÄBERGER, G.: Beiträge zur Kentniss der basalen paramediastinalen Dreieckschatten, Acta. radiol., 1931, *12*, 240.

(9) BLADES, B., AND DUGAN, D.: Tuberculoma of the posterior mediastinum, Am. Rev. Tuberc., 1944, *50*, 41.

(10) EPPLEN, F., AND JACOBSON, A. L.: Twisted pedicle of accessory lobe of lung, J. A.-M. A., 1930, *94*, 1135.

(11) Schaffner, G.: Über den lobus inferior accessorius der menschlichen Lunge., Arch. f. path Anat., 1898, *152*, 1.
(12) Davies, D. V., and Gunz, F. W.: Two cases of lower accessory lung in the human subject, J. Path. & Bact., 1944, *56*, 417.
(13) Bremer, J. L.: Accessory bronchi in embryos: Their occurrence and probable fate, Anat. Rec., 1932, *54*, 361.
(14) Jordan, H.: Two similar cases of an anomalous lobe of lung tissue not attached to the respiratory system, together with a proposed classification of respiratory anomalies, Anat. Rec., 1939, *73*, Supp., page 69.
(15) Ribbert, H.: Zur Kentniss der Tractions-Divertikel des Oesophagus, Arch. f. path. Anat., 1867, *58*, 172. Also cit: Rouvillois and Delater (31) and Bert and Fischer (34).
(16) Mackmull, G.: The relation of anatomical variations to physical diagnosis. 1. The physical signs incident to an accessory pulmonary lobe (azygos lobe), Am. Rev. Tuberc., 1930, *22*, 286.
(17) Muus, M.: Eine Geschwulst der Pleura, von aberrierenden Lungengewebe ausgegangen, Virchows Arch., 1904, *176*, 180.
(18) Mohr, R.: Über Flimmerepithelcysten des Oesophagus, Beitr. z. path. Anat. u. z. allg. Path., 1909, *14*, 333.
(19) Eppinger, H., and Schauenstein, W.: Krankheiten der Lungen, Ergebn. d. allg. Path. u. path. Anat., 1902, *8*, 257. Also cit: Rouvillois and Delater (31) and Bert and Fischer (34).
(20) Henke, F., and Lubarsch, O.: Handbuch. d. spez. pathol. Anat. u. Histol., 1928, Band. 3, Erster Teil, Die Nebenlungen, S.
(21) Cockayne, E. A., and Gladstone, R. J.: A case of accessory lungs associated with hernia through a congenital defect of the diaphragm, J. Anat., 1917–18, *52*, 64.
(22) Stilling, H.: Eine Flimmercyste des mediastinum anticum, Arch. f. path. Anat., 1888, *114*, 557.
(23) Springer, C.: Rudimentäre akzessorische Lunge, Prager. med. Wchnschr., 1898, *23*, 393.
(24) Robsmann, E.: Über retroperitoneal Cysten der Bauchhöle, Königsberg, O. Kummel, 1904.
(25) Child, C. M.: Patterns and Problems of Development, Univ. of Chicago Press, 1941, Ch's. 7, 8, 270 et seq.
(26) Brown, R. K., and Robbins, L. L.: The diagnosis and treatment of bronchiogenic cysts of the mediastinum and lung, Am. J. Thoracic Surg., 1944, *13*, 84.
(27) Imber, I.: A tumor occurring in the superior pulmonary sulcus, Am. J. M. Sc., 1944, *207*, 654.
(28) Humphrey, L.: Accessory lobe of the left lung, J. Anat. & Physiol., London, 1884–85, *19*, 345.
(29) Darier, J.: Étude histologique d'une lobe pulmonaire supplémentaire sans connexion avec le poumon, Bull. Soc. Anat. de Paris, 1888, *63*, 892.
(30) Hugenin and Sorel: Lobe accessoire du poumon gauche chez un enfant de 16 mois, mort du croup et bronchopneumonie de ce lobe, Bull. et. mem. de la Soc. anat. de Paris, 1888, *63*, 862.
(31) Rouvillois, H., and Delater, G.: Lobe pulmonaire aberrant tuberculisé simulant une tumeur du mediastin, Ann. d'Anat. pathol. méd. Chir., 1924.
(32) Farber, Sidney, Depts. of Pathol., Harvard Medical School and of the Children's Hospital, Boston: Written communication and section of anomaly, 1945.
(33) Kent, E. M. *et al.*: Intrathoracic neurogenic tumors, J. Thoracic Surg., 1944, *13*, 116.
(34) Bert, P., and Fischer, B.: Über Nebenlungen und versprengte Lungenkeime, Frankf. Ztschr. f. Path., 1910, *6*, 27.
(35) Zenker: cit: Rouvillois and Delater (31) and Bert and Fischer (34).

(36) EPPINGER, H.: cit: Rouvillois and Delater (31) and Bert and Fischer (34).

(37) CORNER, C. W.: A well preserved human embryo of ten somites, Contrib. to Embryo., Carnegie Instit., Washington, D. C., 1929, *20*, 81.

(38) NEEDHAM, J.: Chemical Embryology, 3 vols., Cambridge Univ. Press, 1931, Vol. 1, 544 et seq.

(39) TYSON, M. D.: The surgical management of solitary cysts, or cyst-like structures of pulmonary origin, Ann. Surg., 1943, *118*, 50. Abstracted in Am. Rev. Tuberc., Abstracts, 1945, *41*, 4.

(40) ZINGG, A.: Mediastinal dermoid, Schweiz. med. Wchnschr., 1943, *73*, 1440. Abstracted in Am. Rev. Tuberc., Abstracts, 1945, *41*, 18.

THE EFFECT OF PURIFIED FRACTIONS OF TUBERCULIN ON TUBERCULIN-SENSITIVE TISSUE

Quantitative Studies on Tissue Cultures

DOROTHY H. HEILMAN[1] AND FLORENCE B. SEIBERT[2, 3]

Tissue culture studies have shown that Old Tuberculin has a selective toxic action on cells from tuberculous animals (1 to 6). In recent years several fractions have been isolated from Old Tuberculin in highly purified form. Among these are purified protein derivative (PPD), tuberculin polysaccharide, and tuberculin nucleic acid, the three chief colloidal constituents of tuberculin. The preparation of PPD has been described by Glenn and one of us (Seibert) (7) and the biological and physicochemical properties of the tuberculin protein, nucleic acid and polysaccharide molecules have been described by Pedersen, Tiselius and one of us (Seibert (8)). It was found that purified protein derivative fractions were generally very active in producing the typical tuberculin reaction in sensitized animals, whereas purified polysaccharide of tuberculin did not cause skin reactions in tuberculous guinea pigs and was not toxic when injected intraperitoneally into either normal or tuberculous guinea pigs. McCarter and Watson (9) showed that, when positive reactions occurred in sensitive human subjects after the intracutaneous injection of large amounts of tuberculin polysaccharide, the reactions observed could be accounted for by the concentration of tuberculin protein present in the preparation. Sabin, Joyner and Smithburn (10) also pointed out the lack of toxicity for tuberculous guinea pigs of purified polysaccharide prepared by Dr. R. J. Anderson from tubercle bacilli. Tuberculin nucleic acid does not appear to cause a reaction in tuberculous animals, after either intraperitoneal or intracutaneous injection. The isolation of tuberculin nucleic acid by partial chemical separation and electrophoresis has been described by Watson and one of us (Seibert (11)). Studies on the chemical and biological characteristics of the three constituents of tuberculin under investigation in this study have been reviewed recently by one of the authors (Seibert (12)).

By the use of quantitative tissue culture methods it is possible to observe the relative toxicity of derivatives of the tubercle bacillus or its products for cells of normal and tuberculous animals. A convenient method for this purpose is one similar to the method described by Moen and Swift (4), in which measurements are made of the migration of wandering cells and the growth of fibroblasts from splenic explants of normal and tuberculous rabbits in plasma clot preparations.

EXPERIMENTAL METHODS

The purified fractions of the tuberculin used in this study were prepared by one of us (Seibert).

[1] Division of Clinical Pathology, Mayo Clinic, Rochester, Minnesota.

[2] The Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

[3] Aided by a grant from the Committee on Medical Research of the National Tuberculosis Association.

Preparation of the purified derivatives of tuberculin: PPD63 was prepared from an eight weeks old growth on Long's synthetic medium of the human strain C of *Mycobacterium tuberculosis* obtained from the Bureau of Animal Industry of the United States Department of Agriculture. The culture was heated in an Arnold sterilizer for two hours and the bacillary growth was removed by filtration first through a paper and then a Seitz filter. The filtrate was concentrated and washed with phosphate buffer by ultrafiltration

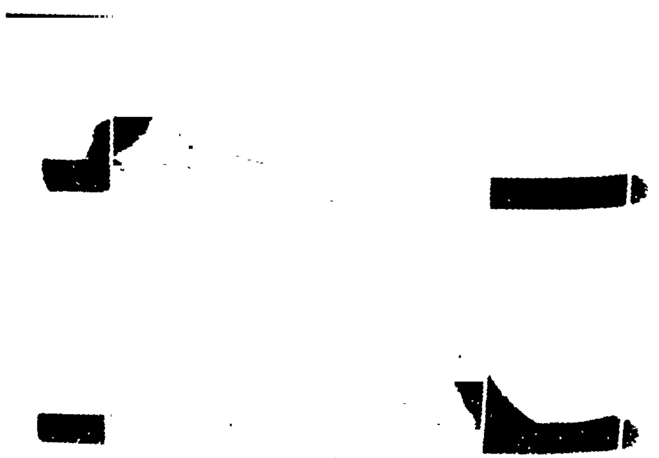


FIG. 1. (Upper) Electrophoretic diagram of PPD 63 in veronal buffer, pH 8.6, $\mu = 0.1$, one hundred and twenty minutes at a potential gradient of 8.86. Top curve represents descending and lower curve ascending diagrams. Two proteins A and B are evident in addition to the delta and epsilon effects. Mobilities are A = -4.2 and B = -6.0×10^{-5} cm.^{2} volt^{-1} sec.$^{-1}$

FIG. 2. (Lower) Electrophoretic diagram of polysaccharide no. 70 in veronal buffer pH 8.6, $\mu = 0.1$, one hundred and eighty minutes at a potential gradient of 9.11. Top curve represents ascending and lower curve descending diagram. Mobility of polysaccharide is -0.22×10^{-5} cm.^{2} volt^{-1} sec.$^{-1}$ and only a trace of impurity is evident.

in the icebox. The solution was adjusted to pH 4.8 and saturated with ammonium sulfate. The resulting precipitate was dissolved in phosphate buffer and the precipitation with ammonium sulfate was repeated. This was followed by precipitation with 2 per cent trichloracetic acid. The precipitate was washed many times with 2 per cent trichloracetic acid and was centrifuged each time. It was then put in solution by neutralizing with sodium hydroxide and washed free of sodium trichloracetate on the ultrafilter. The sterile material in phosphate buffer was frozen and dried by the cryochem process.

The resulting product contained 4.4 per cent of nucleic acid and 5.5 per cent of polysaccharide. A 1.27 per cent solution of the dried PPD in phosphate buffer was made with sterile distilled water and kept in the icebox. Suitable dilutions of the stock solution were made in Tyrode's solution just before use. The concentrated stock solutions were used for as long a period as six months. This preparation, when studied by means of the Tiselius electrophoresis apparatus, showed (figure 1) the presence of the two types (A and B) tuberculin protein found in all tuberculins so far studied and discussed in a recent publication (12).

A limited number of tests was done with another purified preparation of PPD (PPD 49609). This was prepared from an eight weeks old growth on Dorset's synthetic medium of the human strain DT of *Mycobacterium tuberculosis* obtained from the Bureau of Animal Industry of the United States Department of Agriculture. Since this product was the pilot preparation for the standard purified protein derivative, the fractionation was exactly as described previously (7). The electrophoretic diagram is also given in that paper. As noted, the content of nucleic acid was 1.7 per cent and that of polysaccharide was only 2.9 per cent.

A solution of dried PPD49609 containing 0.1 per cent of PPD was made with sterile distilled water and kept in the icebox. Suitable dilutions of the stock solution were made in Tyrode's solution just before use.

For comparison a few tests were done with PPD manufactured for intracutaneous testing by the Mulford Laboratories of Sharp and Dohme. Tablets containing 0.05 mg. of PPD and $\frac{1}{4}$ grain (0.016 g.) of beta-lactose were dissolved in Tyrode's solution and added to the tissue culture medium in the desired amount. The earlier preparations of PPD, made by trichloracetic acid precipitation, of which this was one, frequently contained as much as 17 to 25 per cent of polysaccharide and nucleic acid. The method of its preparation has been described by Reichel and Clark (13).

The purified polysaccharide (no. 70) made from the human strain DT was isolated from a trichloracetic acid filtrate of tuberculin by the chemical procedure described by Renfrew (14) and modified by Masucci, McAlpine and Glenn (15). The solution was neutralized with sodium hydroxide, concentrated *in vacuo* at 50°C. and precipitated with neutral lead acetate. The precipitate was removed by centrifugation and discarded. The supernatant was concentrated *in vacuo* and precipitated with basic lead acetate and concentrated ammonia until no more precipitate formed. The precipitate was dissolved in dilute acetic acid and reprecipitated three more times in the same way. Finally it was dissolved in dilute acetic acid and precipitated with an equal volume of methyl alcohol. The precipitate was discarded and the supernatant was again precipitated by basic lead acetate and ammonia. The precipitate, after being dissolved in dilute acetic acid, was treated with hydrogen sulfide. The precipitate was removed and the supernatant dropped into absolute ethyl alcohol. The white precipitate was dissolved in the smallest amount possible of water, dropped into glacial acetic acid, redissolved in the water, treated with aluminum oxide, centrifuged and again precipitated by dropping into glacial acetic acid and then into absolute alcohol. The white precipitate was dried by repeated washing with absolute alcohol and then acetone. The nitrogen content of this preparation was 0.43 per cent, probably indicating a protein content of about 2.6 per cent. The electrophoretic diagram is shown in figure 2. A stock solution containing 0.2 per cent polysaccharide was made with sterile Tyrode's solution and further dilutions were made in Tyrode's solution just before use.

The sample of tuberculin nucleic acid (S5-1A) used in this study was prepared from the DT human strain of tubercle bacillus by one of us (Seibert) by a method that has been

described (11). This fraction was isolated by electrophoresis in the top anode cell and the final solution contained 8.4 mg. nucleic acid and 0.325 mg. protein per cubic centimeter. The electrophoretic diagram of this nucleic acid preparation is shown in the paper mentioned previously. A solution of the material in phosphate buffer was frozen and dried by the cryochem process. Sterile water was added to the dried material to obtain a 0.4 per cent solution of nucleic acid. Because the solution was not bacteriologically sterile, one portion was heated in a water bath at 70° C. for thirty minutes on two successive days. This portion was used in the first three experiments. Another portion was sterilized by passage through a Seitz filter and was employed in experiments 4 to 9 inclusive. Both lots proved to be sterile when subcultured on bacteriological media.

Tissue culture methods: The tissue culture technique employed in this study and the method of inducing experimental tuberculosis in rabbits have been previously described in detail (6). A mild tuberculous infection was produced in rabbits by the intravenous injection of a culture of *Mycobacterium tuberculosis* of the human type. Tuberculous rabbits were shown to have a positive reaction to the intracutaneous inoculation of 1 mg. of Old Tuberculin within two weeks of the time they were used for tissue culture studies.

Blood used in the preparation of tissue culture medium was obtained from normal rabbits exclusively. Explants of the spleen of a normal rabbit and of that of a tuberculous rabbit were cultured on the same day in medium containing the test substance (PPD, polysaccharide or nucleic acid) as well as in normal medium. Cultures were placed in D5 Carrel flasks and consisted of 0.5 cc. of rabbit's plasma, 1.0 cc. of a rabbit's serum extract of chick embryos and four explants of spleen placed in the medium before clotting occurred. Three flasks, or a total of twelve fragments, were used for each experimental condition.

Dilutions of the substance to be tested were made in Tyrode's solution and were added to the serum-chick-embryo extract before the cultures were made in an amount equal to a twentieth of the volume of the final tissue culture clot. Several different concentrations of PPD63 were employed in order to observe the effect of varying amounts of this substance on the relative inhibition of tuberculin-sensitive cells. From one to four different concentrations of PPD63 were tested on the same day. Two tests were done with each of two different concentrations of PPD manufactured for intracutaneous testing; however, higher concentrations than these were not used because of the relatively large amount of beta-lactose present. One test was done with each of four different concentrations of PPD49609.

Not more than two different concentrations of tuberculin polysaccharide or nucleic acid were tested in an experiment. However, a series of normal and test cultures containing Old Tuberculin was included in each of these experiments to ascertain the tuberculin sensitivity of the test cultures. The sample of tuberculin used was preservative-free mammalian tuberculin of Old Tuberculin strength obtained from the Bureau of Animal Industry of the United States Department of Agriculture. This lot was designated as sample B in a previous report (6) and was used in a concentration of 1:1,000.

Cultures were incubated at 37° C. and were observed microscopically each day. Measurements of the extent of migration of small wandering cells were made at twenty-four hours of incubation and of large wandering cells at ninety-six hours according to a method described previously (6). The growth of fibroblasts was measured on the fifth or sixth day and the average radius of the zone of fibroblastic growth was determined for each series of cultures in a manner already described. The extent to which migration or growth of cells from explants from tuberculous animals occurred in medium containing tuberculin or one of its derivatives was compared with the extent of migration of normal cells in the

same medium.. The results were expressed in terms of a comparative cytotoxic index, which was determined by the following formula:

$$\text{Comparative cytotoxic index} = \frac{\text{Av. migration (N)}}{\text{Av. migration (N + test substance)}} \times \frac{\text{Av. migration (S + test substance)}}{\text{Av. migration (S)}}$$

in which N = cells from normal tissue and S = cells from tuberculin-sensitive tissue. A value less than one indicates that cells from the tuberculous animal are more sensitive to the test substance than normal cells, whereas a value greater than one shows that they are less sensitive than normal cells.

RESULTS

The appearance of cultures of rabbit's spleen at various times during the period of observation has been described in detail (6). In a series of experiments with normal tissue the variation in migration of small wandering cells did not exceed 10 per cent when two groups of cultures in the same experiment were compared. The maximal variation observed for macrophages was 8 per cent and the variation of fibroblastic cultures was at times as high as 20 per cent (6).

The comparative cytotoxic indices expressing the relative effect of different concentrations of PPD on migration of macrophages from splenic explants from normal and tuberculous rabbits are presented in chart 1. In all instances PPD in varying concentrations had a specific toxic action on cultures of explants from tuberculous rabbits. Small wandering cells and fibroblasts resembled macrophages in the extent to which they were inhibited by different concentrations of PPD. Normal macrophages were not inhibited by PPD except in cultures containing 30 micrograms per cubic centimeter or more. The migration of normal macrophages was decreased 20 per cent by 30 micrograms per cubic centimeter and 25 per cent by 60 micrograms per cubic centimeter. Although there was a rather large degree of variation of the relative inhibition caused by the same concentration of PPD in different experiments, a broad quantitative relation existed between the degree of inhibition of migration of sensitive cells and the concentration of PPD employed. PPD63 and PPD49609 were somewhat more active than commercial PPD. On microscopic examination the changes produced by PPD were similar to those observed in the other study, in which the changes were due to the action of Old Tuberculin (6).

Tuberculin polysaccharide was equally toxic for normal and tuberculin-sensitive cells. The average values obtained for the migration of macrophages in each series of cultures in this group of experiments are presented in table 1 and the comparative cytotoxic indices calculated from these values are presented in table 2. In one instance (experiment 4) the comparative cytotoxic index obtained for the tuberculin polysaccharide appeared to be low enough to indicate a specific toxic action for the test series of cultures. However, the results of other experiments in this group indicate that this preparation of polysaccharide

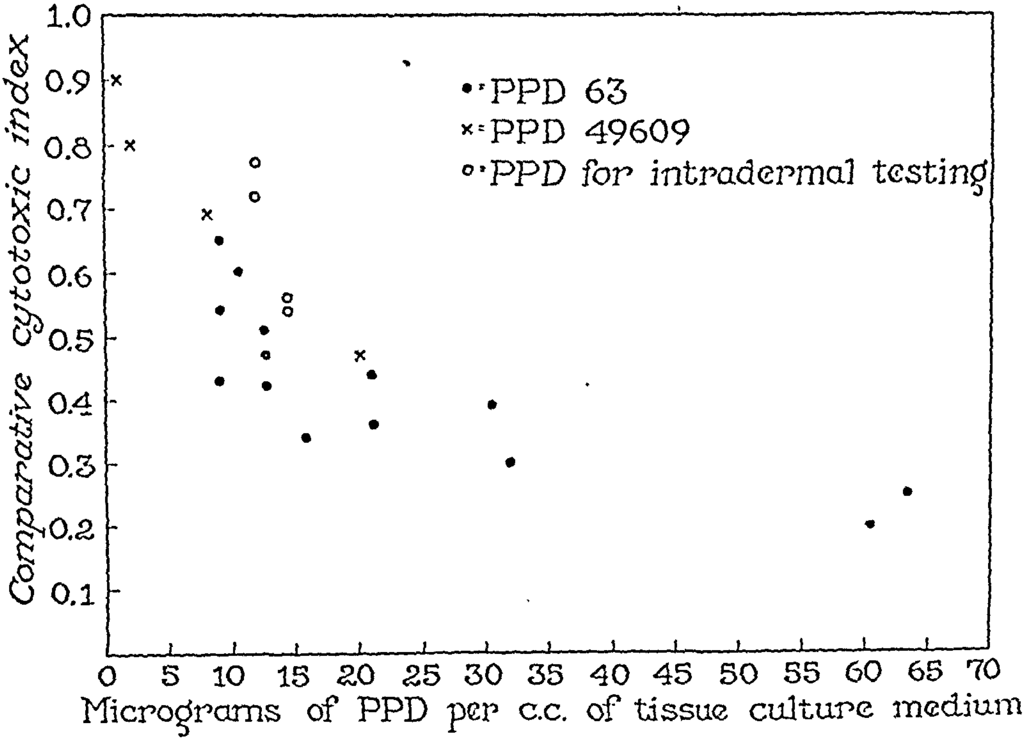


CHART 1. Relation of concentration of purified protein derivative of tuberculin (PPD) to specific cytotoxic action on macrophages from tuberculous rabbits.

TABLE 1

Effect of Old Tuberculin and of tuberculin polysaccharide on migration of macrophages from spleen of normal and tuberculous rabbits. Values given are average radius of migration zone at ninety-six hours in ocular micrometer units

EXPERIMENT	NORMAL MEDIUM		MEDIUM WITH OLD TUBERCULIN		POLYSACCHARIDE, MICROGRAMS PER CUBIC CENTIMETER	MEDIUM WITH POLYSACCHARIDE	
	Normal explants	Test explants	Normal explants	Test explants		Normal explants	Test explants
1	242	325	193	105	12.5 25	226 232	313 304
2	359	374	327	151	25	347	332
3	327	358	281	101	12.5 25	326 269	333 301
4	354	461	327	212	25	303	339
5	486	512	474	160	12.5 25	413 358	406 392

was equally toxic for normal and test cultures. It was only moderately toxic for either group of cultures in concentrations of 12.5 and 25 micrograms per cubic centimeter. A test was done with 100 micrograms per cubic centimeter in the medium. The migration of normal macrophages was decreased 36 per cent and the migration of tuberculin-sensitive cells was decreased 48 per cent. The migration of leucocytes was affected to the same extent as that of the large wandering cells. The relative effect of Old Tuberculin and of tuberculin polysaccharide on the growth of fibroblasts is presented in table 3. The results indicated that the

TABLE 2

Comparative cytotoxic effect of Old Tuberculin and of tuberculin polysaccharide on migration of macrophages from explants of spleen of normal and tuberculous rabbits. Comparative cytotoxic index

EXPERIMENT	OLD TUBERCULIN, 1:1,000	TUBERCULIN POLYSACCHARIDE	
		12.5 micrograms per cubic centimeter	25 micrograms per cubic centimeter
1	0.40	1.03	0.98
2	0.44		0.92
3	0.33	0.93	1.02
4	0.50		0.86
5	0.32	0.93	1.04

TABLE 3

Comparative cytotoxic effect of Old Tuberculin and of tuberculin polysaccharide on growth of fibroblasts from explants of spleen of normal and tuberculous rabbits. Comparative cytotoxic index

EXPERIMENT	OLD TUBERCULIN, 1:1,000	TUBERCULIN POLYSACCHARIDE	
		12.5 micrograms per cubic centimeter	25 micrograms per cubic centimeter
1	0.67	0.98	1.02
2	0.62		0.93
3	0.50	1.19	1.18
4	0.31		0.86
5	0.42	0.87	0.98

growth of fibroblasts in the presence of polysaccharide was as good as in control cultures and that growth was not significantly diminished by polysaccharide in either group, as it was in the case of the large wandering cells.

Relatively large amounts of tuberculin nucleic acid could be added to tissue cultures without injuring either normal or tuberculin-sensitive cells. The highest concentration of nucleic acid (400 micrograms per cubic centimeter) caused a slight but significant decrease in migration of macrophages from both normal and tuberculin-sensitive tissues but the growth of fibroblasts was not decreased. Concentrations of 200 micrograms per cubic centimeter or less usually did not cause a significant variation in growth but there was a well-marked increase in

the extent of growth in a few instances in cultures containing 50 to 200 micrograms of nucleic acid. This stimulation was observed both in normal and in test cultures.

TABLE 4

Comparative cytotoxic effect of Old Tuberculin and of tuberculin nucleic acid on the twenty-four hour migration of leucocytes from explants of spleen of normal and tuberculous rabbits. Comparative cytotoxic index

EXPERIMENT	OLD TUBERCULIN, 1:1,000	TUBERCULIN NUCLEIC ACID		
		200 micrograms per cubic centimeter	100 micrograms per cubic centimeter	50 micrograms per cubic centimeter
3	0.40	1.01		
4	0.84	1.16		
6	0.71	1.13	1.06	
7	0.79	1.01		1.11
8	0.62		1.10	1.15
9	0.60		1.19	1.07

TABLE 5

Comparative cytotoxic effect of Old Tuberculin and of tuberculin nucleic acid on the migration of macrophages from explants of spleen of normal and tuberculous rabbits. Comparative cytotoxic index

EXPERIMENT	OLD TUBERCULIN 1:1,000	TUBERCULIN NUCLEIC ACID			
		400 micrograms per cubic centimeter	200 micrograms per cubic centimeter	100 micro grams per cubic centimeter	50 micrograms per cubic centimeter
1	0.64	1.18	0.99		
2	0.51	0.82	0.94		
3	0.69		1.03		
4	0.76		1.16		
5	0.37	1.06	1.11		
6	0.57		1.00	1.01	
7	0.40		1.01		1.24
8	0.29			1.10	0.98
9	0.38			0.93	0.92

Tuberculin nucleic acid did not have a specific cytotoxic action on any of the cell types observed in splenic cultures. The relative migration of small wandering cells from tuberculin-sensitive tissue in the presence of nucleic acid was somewhat greater in every instance than that of small cells from normal tissue (table 4). However, the differences were slight and within normal limits of variation. Measurements of migration of small wandering cells were not made in the first, second and fifth experiments. Cells found in the migration zone at twenty-four hours of incubation are largely granulocytes and lymphocytes. Granulocytes usually predominate, especially at the periphery of the migration zone. Results obtained with large wandering cells (table 5) and fibroblasts

(table 6) indicated that the effect of tuberculin nucleic acid on tuberculin-sensitive tissue was not significantly different from its effect on normal tissue. In a few experiments the fibroblastic growth pulled away from the clot and measurements could not be made.

TABLE 6

Comparative cytotoxic effect of Old Tuberculin and of tuberculin nucleic acid on the growth of fibroblasts in cultures of spleen of tuberculous and normal rabbits. Comparative cytotoxic index

EXPERIMENT	OLD TUBERCULIN 1:1,000	TUBERCULIN NUCLEIC ACID			
		400 micrograms per cubic centimeter	200 micrograms per cubic centimeter	100 micrograms per cubic centimeter	50 micrograms per cubic centimeter
1	0.62	1.25	1.27		
2	0.36	0.95	1.03		
4	0.64		1.03		
6	0.37		1.14	1.07	
8	0.54			1.02	1.08
9	0.51			0.91	0.80

COMMENT

The biological importance of the protein derivative of tuberculin in demonstrating tuberculin sensitivity of animals and the lack of specificity of the purified polysaccharide and nucleic acid fractions are reflected in the behavior of these substances in tissue culture. The toxic action of PPD for tuberculin-sensitive tissue was roughly proportional to the concentration of this substance in the tissue culture medium, in spite of the variation that exists in the degree of tuberculin sensitivity of tissues from different tuberculous rabbits. The concentration of Old Tuberculin used in this study (1:1,000) had about the same specific cytotoxic activity as approximately 10 micrograms per cubic centimeter of PPD63, indicating that PPD63 is about one hundred times as active as this sample of Old Tuberculin. There is often a great difference in the activity of different lots of Old Tuberculin when they are tested in tissue culture. Two lots of Old Tuberculin in particular have been studied by us in splenic cultures. The crude tuberculin used in the present study (sample B) has been found to be twice as active as sample A, which was used earlier (6). In other words PPD63 is approximately two hundred times as active as sample A. This is in agreement with the relative tuberculin activity of PPD and OT determined by intracutaneous tests.

All three preparations of PPD appeared to be relatively nontoxic for normal tissue. Although extensive comparative tests were not made, results obtained in the present study would indicate that PPD63 and tuberculin polysaccharide (no. 70) are of the same order of toxicity for normal splenic tissue. This may account in part for the greater nonspecific toxicity of Old Tuberculin (that is, toxicity for normal tissue) than that of PPD compared with the relative amount of each substance that is toxic for tuberculous tissue in tissue culture.

The positive chemotactic activity of tuberculin polysaccharide for granulocytes described by Sabin, Joyner and Smithburn (10) could not be demonstrated with the method used in the present study. This method is useful for studying cytotoxicity, but is not suitable for demonstrating positive chemotaxis, because the test substance is distributed evenly throughout the medium. The suggestion made by Sabin, Joyner and Smithburn (10) that tuberculin polysaccharide may not be entirely nontoxic is substantiated by results obtained in the present study. An example of the nontoxicity of a simple carbohydrate was seen in the behavior of beta-lactose present in large amounts in cultures in which PPD for intracutaneous use was tested. A concentration of 1:200 of beta-lactose in the medium did not decrease the migration of macrophages from normal explants.

Cultures containing the highest concentration of tuberculin polysaccharide in the present study (25 micrograms per cubic centimeter) also contained 0.65 microgram per cubic centimeter of tuberculin protein. This concentration of protein would appear to be too small to cause a specific cytotoxic effect. On the other hand, the highest concentration of tuberculin nucleic acid used contained 15 micrograms of protein, an amount that would be expected to decrease the migration of sensitive macrophages approximately 50 per cent. This would seem to indicate that the protein that is firmly bound to the nucleic acid fraction is not as active as other protein components found in tuberculin. As a matter of fact, these conclusions are valid in view of results previously recorded. For example, it was clearly shown (8) that the protein with the slower mobility in electrophoresis, and later (12) designated as the A type protein, had greater potency than the B type, which migrated with a faster mobility. It is the A type protein that would accompany the polysaccharide fraction and the B type that would accompany the nucleic acid. The relative potency of these two types of protein will be studied quantitatively in the future.

The stimulation of growth and migration of cells in some of the cultures containing tuberculin nucleic acid was of considerable interest. Reports dealing with the growth-stimulating properties of nucleic acid and nucleoproteins are too numerous to include in this discussion. Further studies will be carried out to determine the effect of lower concentrations of nucleic acid in order to determine whether or not this fraction may play a significant rôle in the disease process in tuberculosis.

SUMMARY AND CONCLUSIONS

As a part of a study of the specific cytotoxic action of tuberculin on cells from tissues of tuberculous animals, the rôle of some of the purified fractions of tuberculin has been investigated The presence of purified protein derivatives of tuberculin in very small amounts in cultures of spleen from tuberculous rabbits caused a significant decrease of the migration of wandering cells and the growth of fibroblasts, whereas normal cells were not affected. The samples of PPD tested were very similar to each other in activity, and were about one hundred times as active as one sample of Old Tuberculin and two hundred times as active as another sample of Old Tuberculin tested by the same method.

Purified tuberculin polysaccharide and nucleic acid did not have a specific toxic action for tuberculous tissue. The protein accompanying the nucleic acid fraction was not as active in producing the specific cytotoxic reaction as other protein derivatives of tuberculin that have been tested.

Tuberculin polysaccharide had a relatively low toxicity for both normal and tuberculin-sensitive tissues. The toxicity of tuberculin polysaccharide for splenic tissue of the normal rabbit was of the same order as that of PPD.

No evidence of toxicity resulted from the highest concentration of tuberculin nucleic acid that could be employed. In some instances the growth of both normal and tuberculin-sensitive cells was stimulated by tuberculin nucleic acid.

SUMARIO Y CONCLUSIONES

Como parte de un estudio de la acción citotóxica específica ejercida por la tuberculina sobre las células de los tejidos de los animales tuberculosos, se investigó el papel de algunas de las fracciones purificadas de dicha sustancia. La presencia de cantidades pequeñísimas de derivados proteínicos purificados de la tuberculina en los cultivos esplénicos de los conejos tuberculosos provocó una disminución significativa de la migración de las células errantes y de la proliferación de fibroblastos, en tanto que no afectó las células normales. Las muestras de PPD comprobadas mostraron una actividad muy semejante, siendo unas cien veces más activas que una muestra de tuberculina antigua y doscientas veces más que otra muestra de tuberculina antigua comprobada con la misma técnica.

El polisacárido y el ácido nucleico de tuberculina purificados no mostraron acción tóxica específica sobre el tejido tuberculoso. La proteína que acompañaba a la fracción de ácido nucleico no se mostró tan activa en producir la reacción citotóxica específica como otros derivados proteínicos de la tuberculina que fueron comprobados.

El polisacárido de la tuberculina mostró una toxicidad bastante baja tanto para los tejidos normales como para los tuberculino-sensibles. La toxicidad del mismo para el tejido esplénico del conejo normal fué del mismo género que la de PPD.

No se observaron signos de toxicidad con el ácido nucleico de la tuberculina a la concentración máxima que pudo emplearse, y en algunos casos dicha sustancia estimuló la proliferación de las células tanto normales como tuberculino-sensibles.

REFERENCES

(1) Rich, A. R., and Lewis, Margaret R.: The nature of allergy in tuberculosis as revealed by tissue culture studies, Bull. Johns Hopkins Hosp., 1932, *50*, 115.

(2) Aronson, J. D.: The specific cytotoxic action of tuberculin in tissue culture, J. Exper. Med., 1931, *54*, 387.

(3) Aronson, J. D.: Tissue culture studies on the relation of the tuberculin reaction to anaphylaxis and the Arthus phenomenon, J. Immunol., 1933, *25*, 1.

(4) Moen, J. K., and Swift, H. F.: Tissue culture studies on bacterial hypersensitivity. I. Tuberculin sensitive tissues, J. Exper. Med., 1936, *64*, 339.

(5) Moen, J. K.: Tissue culture studies on bacterial hypersensitivity. III. The persistence in vitro of the inherent sensitivity to tuberculin of cells from tuberculous animals, J. Exper. Med., 1936, *64*, 943.

(6) Heilman, Dorothy H., Feldman, W. H., and Mann, F. C.: Specific cytotoxic action of tuberculin: Quantitative studies on tissue cultures, Am. Rev. Tuberc., 1944, *50*, 344.
(7) Seibert, Florence B., and Glenn, J. T.: Tuberculin purified protein derivative: Preparation and analyses of a large quantity for standard, Am. Rev. Tuberc., 1941, *44*, 9.
(8) Seibert, Florence B., Pedersen, K. O., and Tiselius, Arne: Molecular weight, electrochemical and biological properties of tuberculin protein and polysaccharide molecules, J. Exper. Med., 1938, *68*, 413.
(9) McCarter, Janet R., and Watson, D. W.: The relationship of the antigenicity, physical-chemical properties, and polysaccharide-content of tuberculins to their intracutaneous activity, J. Immunol., 1942, *43*, 85.
(10) Sabin, F. R., Joyner, A. L., and Smithburn, K. C.: Cellular reactions to polysaccharides from tubercle bacilli and from pneumococci, J. Exper. Med., 1938, *68*, 563.
(11) Seibert, Florence B., and Watson, D. W.: Isolation of the polysaccharides and nucleic acid of tuberculin by electrophoresis, J. Biol. Chem., 1941, *140*, 55.
(12) Seibert, F. B.: Chemistry of tuberculin, Chem. Rev., 1944, *34*, 107.
(13) Reichel, J., and Clark, L. T.: Manufacture of purified protein derivative of tuberculin, Am. Rev. Tuberc., 1934, *30*, 721.
(14) Renfrew, Alice G.: The chemical study of bacteria. XXIX. A proximate analysis of a defatted residue of avian tubercle bacilli, J. Biol. Chem., 1929, *83*, 569.
(15) Masucci, Peter, McAlpine, K. L., and Glenn, J. T.: Biochemical studies of bacterial derivatives. XII. The preparation of human tubercle-bacillus polysaccharide MB-200 and some of its biological properties, Am. Rev. Tuberc., 1930, *22*, 669.

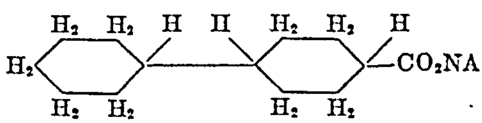
THE TUBERCULOSTATIC ACTION OF THE SODIUM SALTS OF CERTAIN SYNTHETIC ALICYCLIC ACIDS[1]

E. W. EMMART

The early investigations of Walker and Sweeney (1, 2, 3) in experimental tuberculosis demonstrated that, while chaulmoogra oil and its principal component chaulmoogric acid were effective *in vitro* against the tubercle bacillus, the therapeutic effectiveness of these compounds in experimental animals was doubtful. In an extensive series of investigations with tuberculous guinea pigs Voegtlin, Smith and Johnson (4) also obtained negative results with chaulmoogra oil and its derivatives. In spite of these failures the specificity of chaulmoogric acid for acid-fast organisms *in vitro* (1) suggests that other new derivatives or related compounds might be of value in the treatment of tuberculosis. More recently Wagner-Jauregg (5) claims to have obtained slight therapeutic effectiveness in guinea pigs with nine different esters of chaulmoogric acid. Prigge (6, 7) also obtained inhibition of growth of the tubercle bacillus *in vitro* with a series of esters of chaulmoogric acid and chaulmoogryl alcohol. These studies were continued further *in vivo* by Arnold and his associates (8) who attempted to determine the effects of long chain fatty acids in combination with sulfanilamide and sulfapyridine in the oral treatment of experimental tuberculosis in guinea pigs and mice. These compounds, however, proved to be ineffective under their experimental conditions.

The present report deals with the tuberculostatic properties of the sodium salts of certain alicyclic acids[2] which have been tested both *in vitro* and *in vivo*, using the chorio-allantoic membrane of the chick embryo as a test object. For comparison, preliminary *in vitro* tests were also carried out with the sodium salt of chaulmoogric acid ($C_{18}H_{32}O_2$).[3] The chemical structure of the various alicyclic compounds used is given below together with concentration of solutions as received. For the sake of brevity they are designated in the tables and charts by letters and the concentration of the stock solutions given as follows:

Sodium-4-cyclohexylcyclohexane carboxylate—($C_{13}H_{21}O_2Na$)—"J"—0.03 N

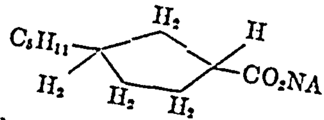


[1] From the Division of Physiology, National Institute of Health, U. S. Public Health Service, Bethesda, Maryland.

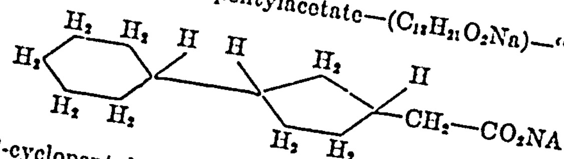
[2] All sodium salts of these alicyclic compounds were prepared and supplied by K. M. Seymour and H. Posvic. Most of the work on the preparation of the compounds was done at Carleton College, Northfield, Minnesota.

[3] The sodium chaulmoograte was made from chaulmoogric acid furnished us by Dr. J. M. Johnson (National Cancer Institute, of the National Institute of Health) who isolated it from chaulmoogra oil following the method used by F. B. Power and F. H Gornall, J. Chem. Soc. (London), 1904, *85*, 838.

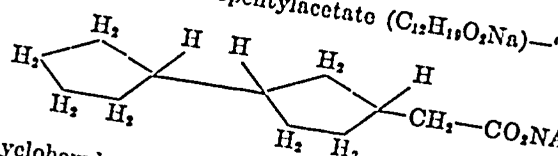
Sodium-3-amyl-cyclopentane carboxylate—($C_{11}H_{19}O_2Na$)—"C"—0.1 N



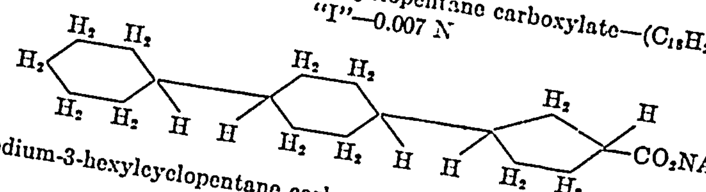
Sodium-3-cyclohexylcyclopentylacetate—($C_{13}H_{21}O_2Na$)—"L"—0.1 N



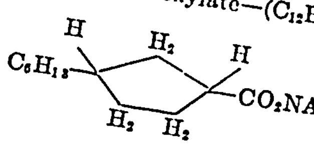
Sodium-3-cyclopentyl-cyclopentylacetate ($C_{12}H_{19}O_2Na$)—"K"—0.1 N



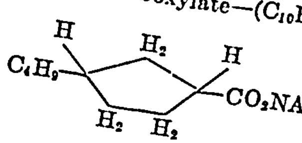
Sodium-3-(4-cyclohexylcyclohexyl)-cyclopentane carboxylate—($C_{18}H_{29}O_2Na$)—
"I"—0.007 N



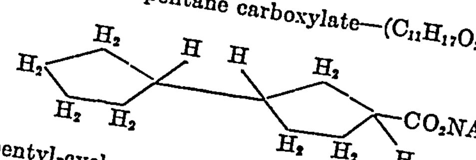
Sodium-3-hexylcyclopentane carboxylate—($C_{12}H_{21}O_2Na$)—"D"—0.1 N



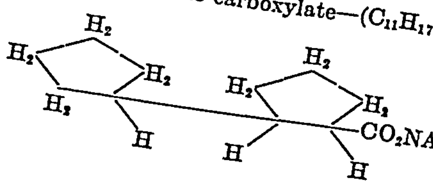
Sodium-3-butylcyclopentane carboxylate—($C_{10}H_{17}O_2Na$)—"B"—0.1 N



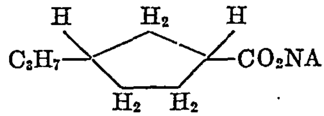
Sodium-3-cyclopentyl-cyclopentane carboxylate—($C_{11}H_{17}O_2Na$)—"G"—0.1 N



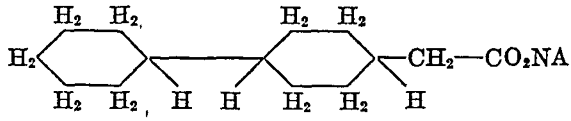
Sodium-2-cyclopentyl-cyclopentane carboxylate—($C_{11}H_{17}O_2Na$)—"F"—0.1 N



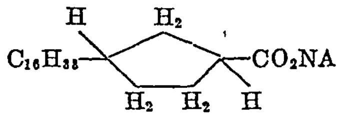
Sodium-3-propyl-cyclopentane carboxylate—($C_9H_{15}O_2Na$)—"A"—0.1 N



Sodium-4-cyclohexyl-cyclohexyl acetate—($C_{14}H_{23}O_2Na$)—"M"—0.02



Sodium-3-hexadecylcyclopentane carboxylate—($C_{22}H_{41}O_2Na$)—"E"—0.01 N



EXPERIMENTAL

The compounds were tested *in vitro* in a medium consisting of Difco beef bouillon plus 5 per cent glycerine and in Kirchner's medium.[4] The preliminary experiments were carried out with 0.5 cc. of stock solution of each drug in 50 cc. of media. Each drug was tested in six flasks each of Difco medium and in three flasks of Kirchner's medium and the average rate of growth recorded for each group. The amount of growth was graded from 0 to 4. Fractions of these figures were evaluated as follows: 1/4 surface of flasks—1.5, 1/2—2.0, 3/4—3.5, and 4 denoting complete surface growth. Since the inoculum is only about 2 mm. in diameter and the surface of the culture medium is about 6.5 cm. considerable growth may occur before it can be evaluated as 1.0, which is approximately 5 mm. in diameter. This arbitrary, though not mathematically exact, system of evaluation has been used consistently throughout, because the rate of growth is greatly accelerated after the preliminary lag period of seven to fourteen days.

After preliminary tests *in vitro* with all the compounds the four most active acids were selected for further detailed study *in vitro* and *in vivo*.

Before testing the compounds for their action *in vivo*, toxicity tests were first carried out to determine the dose at which approximately 50 per cent of the

---

[4] Kirchner's medium:

Dibasic sodium phosphate	3.0 g.
Monopotassium phosphate	4.0 g.
Magnesium sulphate	0.6 g.
Sodium citrate	2.5 g.
Asparagin	5.0 g.
Glycerine	20.0 cc.
Water	1000.0 cc.

(Adjust to pH 7.2 with approximately 2.0 cc. of 40 per cent sodium hydroxide. Autoclave at 10 lbs. pressure for twenty minutes.)

embryos survived. This dose was then used in 0.2 cc. of the inoculum containing 1 mg. of tubercle bacilli. The drug-bacillary suspension was incubated overnight at 37.5°C. and then implanted on the membrane through an opening drilled in the shell of the eight-day old chick embryo. The opening was then sealed with a cover glass and sterile paraffin.

After six days the coverslip was removed and the exposed portion of the chorio-allantoic membrane fixed *in situ*, excised and examined as previously described (9, 10, 11). The number and extent of the development of the tubercles in each membrane were noted. These gross findings were verified by microscopic examination of the sectioned membranes. In all experiments the A27 strain of human tubercle bacilli was used.

RESULTS

Tuberculostatic action of sodium chaulmoograte ($C_{18}H_{32}O_2Na$): The tuberculostatic action of sodium chaulmoograte was tested in concentrations of 2.8, 3.2, 6.5 and 13.0 mg. per cent. In concentrations of 13.0 mg. per cent in Kirchner's medium marked inhibition was obtained, while concentrations of 3.2 and 6.5 mg. per cent had slight, if any, effect. Similarly 13.0 mg. per cent of sodium chaulmoograte produced some inhibition in Difco beef bouillon, but this was less marked than in Kirchner's medium (chart 1). The data shown in chart 1 are similar to those reported by Walker and Sweeney (1) who obtained inhibition of growth of strains of *B. avis*, *B. bovis* and *B. hominis* in broth culture media containing 10.0 mg. per cent of sodium chaulmoograte. The inhibiting action *in vitro* of sodium chaulmoograte in higher concentration than 13 mg. per cent could not be studied because of the limited solubility of the drug.

Tuberculostatic action of the alicyclic compounds in vitro: The twelve alicyclic compounds which were tested for their tuberculostatic properties varied considerably in solubility. They were available in concentrations varying from 2.1 mg. to 23.2 mg. per cc. In some instances the compounds were not available for more than the initial testing *in vitro*. Of the twelve compounds tested, four, sodium-3-hexadecylcylopentane carboxylate ("E"), sodium-3-(4-cyclohexylcyclohexyl)-cyclopentane carboxylate ("I"), sodium-4-cyclohexyl-cyclohexyl acetate ("M") and sodium-4-cyclohexylcyclohexane carboxylate ("J"), were of relatively low solubility while the maximum concentration of the rest ranged from 17.8 to 23.2 mg. per cc.

Chart 2 gives the average growth of the pellicle of tubercle bacilli after twenty-four days in both culture media following the addition of 0.5 cc. of each of the twelve compounds. From these experiments it appears that no significant difference in the growth of the control cultures occurred in the two media, but that considerable variation in growth occurred in the two culture media when the alicyclic compounds were added. Since the pH of the media containing these solutions was adjusted to 7.0 this difference in growth cannot be a pH effect.

Of the twelve compounds, "A", "I", "F", "M" and "E" were the least effective in inhibiting the growth of the tubercle bacillus *in vitro* in the specific

concentration used, and of the remaining seven, the four most effective were selected for more detailed study. The tuberculostatic effect of the compounds "C" and "K" belonging to the cyclopentane series was studied in concentrations of 1.0, 2.0, 5.0 and 10.0 mg. per cent in both media. At concentrations of 1.0 and 2.0 mg. per cent inhibition was slightly greater in Kirchner's medium than in Difco beef bouillon. At concentration of 10 mg. per cent no growth occurred in Difco beef bouillon and slight growth in Kirchner's medium. Compound

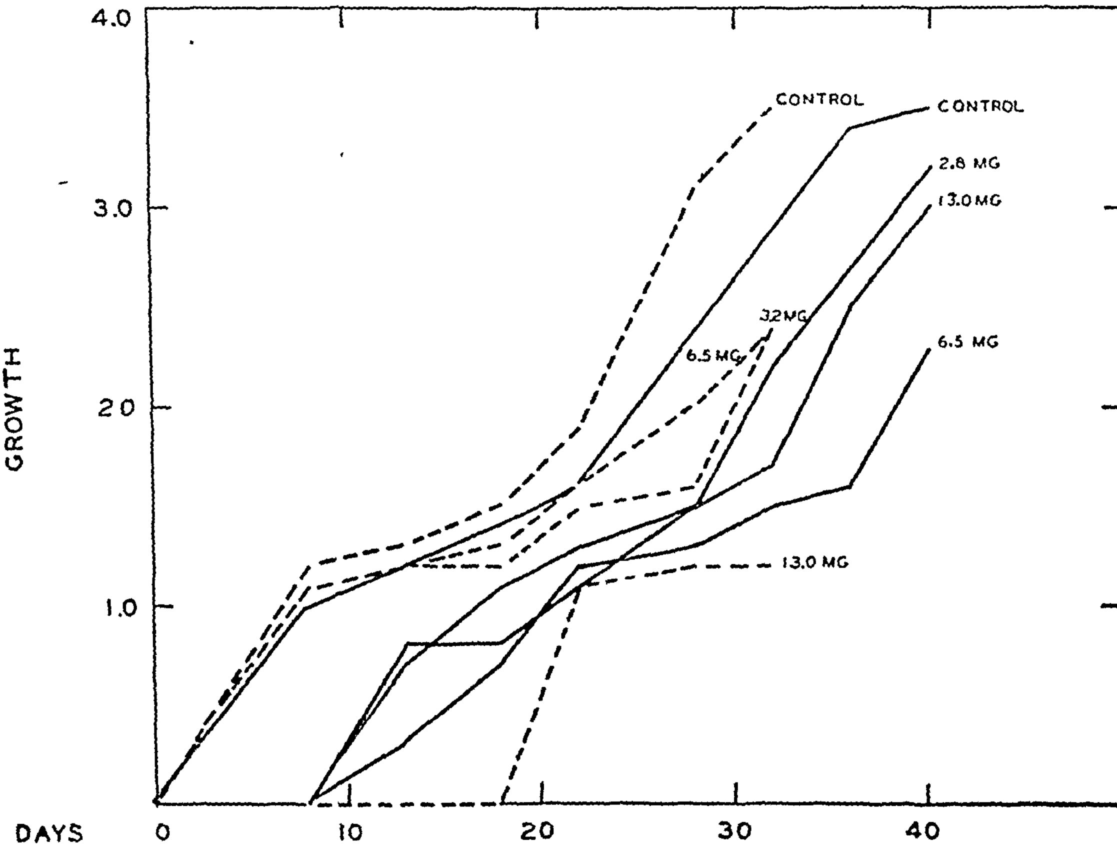


CHART 1. Bacteriostatic effect of sodium chaulmoograte *in vitro*. (Solid lines = Difco beef bouillon, dashes = Kirchner's medium.)

"L" belonging to the same series inhibited growth completely at 5 mg. per cent in Kirchner's medium but permitted fair growth in bouillon. Compound "J" of the cyclohexane series was studied in concentrations of 1.9, 3.8 and 7.7 mg. per cent. No growth was obtained in bouillon at 7.7 mg. per cent and slight growth in Kirchner's medium (chart 3). Compound "D" which was also strongly inhibitory (chart 2) differed from "C" in that it contained a hexyl group in place of an amyl group. The limited amount of the "D" compound, however, precluded its use for further investigations at this time.

Toxicity of the alicyclic compounds to the chick embryo: The four drugs, sodium-4-cyclohexylcyclohexane carboxylate ("J"), sodium-3-amyl-cyclopentane car-

boxylate ("C"), sodium-3-cyclohexylcyclopentylacetate ("L") and sodium-3-cyclopentyl-cyclopentylacetate ("K"), were selected for *in vivo* studies because of their high activity *in vitro*. They were inoculated on the chick membrane in amounts of 1, 2 and 4 mg. to determine approximately the dose which would permit 50 per cent survival. The data in table 1 indicate that in these doses there was little relative difference in the toxicity of the four drugs. Since 1 mg. gave less than 50 per cent survival in three of the drugs and 50 per cent in the case of only one drug, 0.5 mg. was taken as the dose permitting 50 per cent or

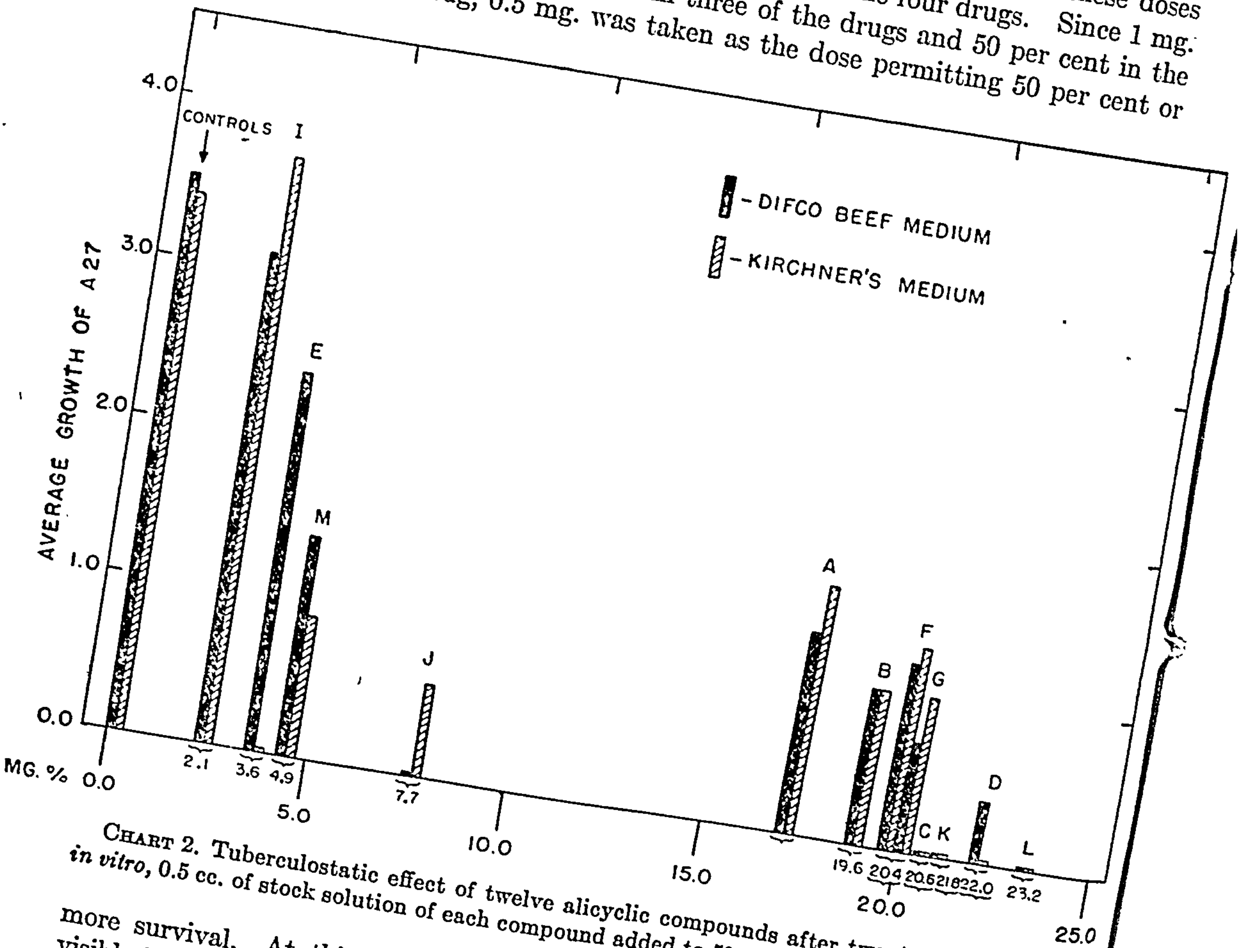


CHART 2. Tuberculostatic effect of twelve alicyclic compounds after twenty-four days *in vitro*, 0.5 cc. of stock solution of each compound added to 50 cc. of medium.

more survival. At this concentration none of the four drugs produced any visible injury to the chorio-allantois.

In studying the tuberculostatic action of these four compounds, after twenty-four hours' exposure of the bacilliary suspension to the drug 42 to 60 eggs were inoculated in each group. The resulting tubercle infection in the surviving chorio-allantoic membranes of each series was then studied in comparison with the respective controls. The degree of effectiveness of each compound was based first upon the incidence of infection in the surviving membranes. In all experiments the incidence of infection in the experimental groups was less than

in the control groups. However, when the chi square test using the "Four Fold Table" formula[5] was applied to these data only "C" and "K" appear to

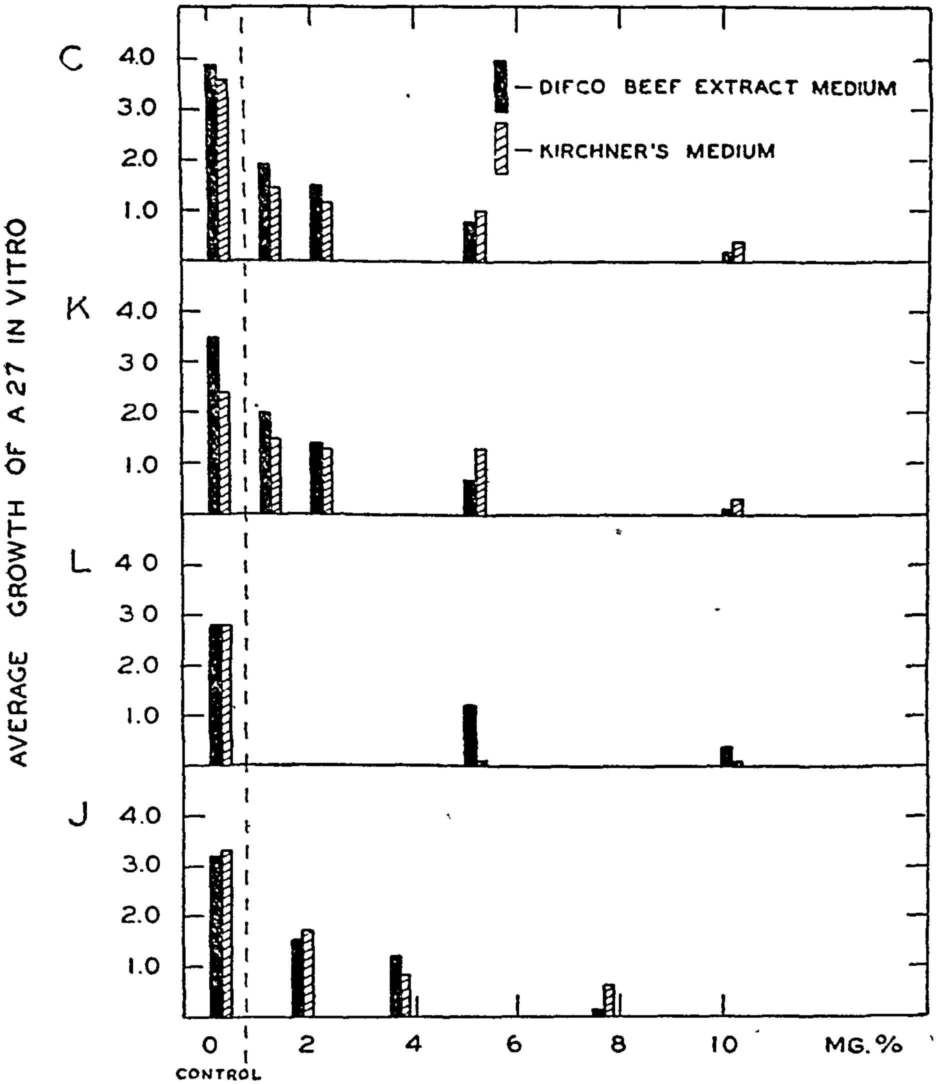


CHART 3. Tuberculostatic effect of "C", "K", "L", and "J" compounds in concentrations of from 2 to 10 mg. per cent after twenty-four days *in vitro*. "C" = Sodium-3-amyl-cyclopentane carboxylate. "K" = Sodium-3-cyclopentyl-cyclopentylacetate. "L" = Sodium-3-cyclohexylcyclopentylacetate. "J" = Sodium-4-cyclohexylcyclohexane carboxylate.

have produced significant[6] results (table 2). Compounds "J" and "L" when judged on this basis appear to have been ineffective.

[5] See footnote 1 in table 2.

[6] Significance as here used denotes that the difference between the percentage of membranes with tubercles in the control and experimental groups was larger than would occur by chance.

TABLE 1

Relative toxicity of "J", "K", "L" and "C" compounds to the developing chick embryo

COMPOUND	DOSE IN MG.	NUMBER OF EGGS INOCULATED	NUMBER OF EGGS SURVIVING	PER CENT SURVIVAL
"J"	4	30	0	0
	2	47	7	14
	1	30	15	50
Control	0	66	43	65
"K"	4	25	0	0
	2	25	7	28
	1	50	22	44
Control	0	82	58	70
"L"	4	33	2	6
	2	39	6	15
	1	24	11	45
Control	0	37	23	62
"C"	4	30	1	3
	2	23	7	30
	1	22	8	36
Control	0	48	24	50

TABLE 2

The effect of "J", "C", "L" and "K" on the incidence and extent of tubercle infection on the chorio-allantoic membrane of the chick embryo

COMPOUND (0.5 MG. PER 0.2 CC. OF BACILLARY SUSPENSION	MEMBRANES INOCULATED	MEMBRANES SURVIVING		SURVIVING MEMBRANES WITH TUBERCLES		"P"—PROBABILITY[1] (SIGNIFICANCE OF PRESENCE OR ABSENCE OF MEMBRANES WITH TUBERCLES)	AVERAGE NUMBER OF TUBERCLES PER SURVIVING MEMBRANE	"P"—PROBABILITY[2] (SIGNIFICANCE OF DIFFERENCES IN AVERAGE NUMBER OF TUBERCLES OF EXPERIMENTAL AND CONTROL GROUPS)
	number	*number*	*per cent*	*number*	*per cent*		*number*	
"J"	45	27	60	24	89	$P = 0.31$	2.0	$P < 0.001$
Control	43	23	51	22	100	(Not significant)	41.1	(Significant)
"C"	49	23	47	15	65	$P = 0.004$	0.9	$P < 0.001$
Control	42	26	62	26	100	(Significant)	23.1	(Significant)
"L"	60	27	45	20	74	$P = 0.14$	0.9	$P < 0.001$
Control	47	20	43	19	95	(Not significant)	10.3	(Significant)
"K"	42	15	36	9	60	$P = 0.03$	1.3	$P < 0.001$
Control	42	14	33	14	100	(Significant)	15.6	(Significant)

[1] The chi square test using "fourfold tables": formula adjusted for small numbers:

$$\text{Chi square} = \frac{(ad-bc-\frac{1}{2}N)^2\,N}{(a+b)\ (c+d)\ (a+c)\ (b+d)}$$

See: Hill, A. B.: Principles of Medical Statistics, The Lancet, Ltd., London, 1937, p. 93.

[2] Significance of difference between two means using "t" distribution since numbers are small. See: Croxton, F. E., and Cowden, D. J.: Applied General Statistics, Prentice Hall, Inc., New York, 1942, p. 330.

The second and more important criterion for the effectiveness of the drug is based upon the average number of tubercles per membrane in each group. In all four series the number of tubercles per membrane is markedly reduced in the experimental groups, and this is especially noted in the membranes which received inoculum containing either sodium-3-amyl-cyclopentane carboxylate ("C") or sodium-4-cyclohexylcyclohexane carboxylate ("J"). Moreover, when the statistical significance of the difference between the average number of

TABLE 3

Extent of development of tuberculous process in the chorio-allantoic membranes

INOCULUM 0 5 MG OF COMPOUND PLUS 1 MG OF A27	NUMBER OF MEMBRANES	MICROSCOPIC ANALYSIS OF TUBERCLE DEVELOPMENT (AVERAGE DEGREE OF DEVELOPMENT EVALUATED 0–4)				AVERAGE NUMBER OF TUBERCLES PER MEMBRANE	GROSS APPEARANCE OF TUBERCLES
		Epithelium	Eosinophils	Monocytes	Tubercles		
"J"	27	0.5	0.6	1.1	0.4	2.0	Mostly small with many vesiculated lesions
Control	22	1.1	1.3	1.6	1.1	41.0	Conglomerate and numerous discrete tubercles
"C"	23	0.4	1.0	1.1	0.3	0.9	Mostly small tubercles and frequently large vesiculated lesions
Control	26	0.9	1.8	2.1	1.9	23.1	Many conglomerate tubercles
"L"	27	1.1	1.3	1.5	0.4	0.9	Small tubercles and a few vesiculated lesions
Control	20	0.7	1.2	1.6	1.0	10.3	Typical tubercles
"K"	15	0.6	1.1	1.4	0.7	1.3	Mostly small, no vesiculated lesions
Control	14	1.1	1.3	1.8	1.6	15.6	Typical tubercles of varying size

tubercles per membrane for each experimental group and the corresponding control was determined by the formula from Croxton and Cowden,[7] the probability in each instance ("P values") that the difference was due to chance was less than one in a thousand; thus on this basis all four drugs appear to have been effective (table 2).[8]

The third criterion for the relative effectiveness of the compounds shown in table 3 is based upon the size of the tubercles, which is greatly reduced by all four drugs but especially in the membranes inoculated with suspensions con-

[7] See footnote 2 in table 2.

[8] The author wishes to acknowledge the assistance of Dr. Selwyn D. Collins, Head Statistician, U S. Public Health Service, for consultation on the statistical aspects of the material.

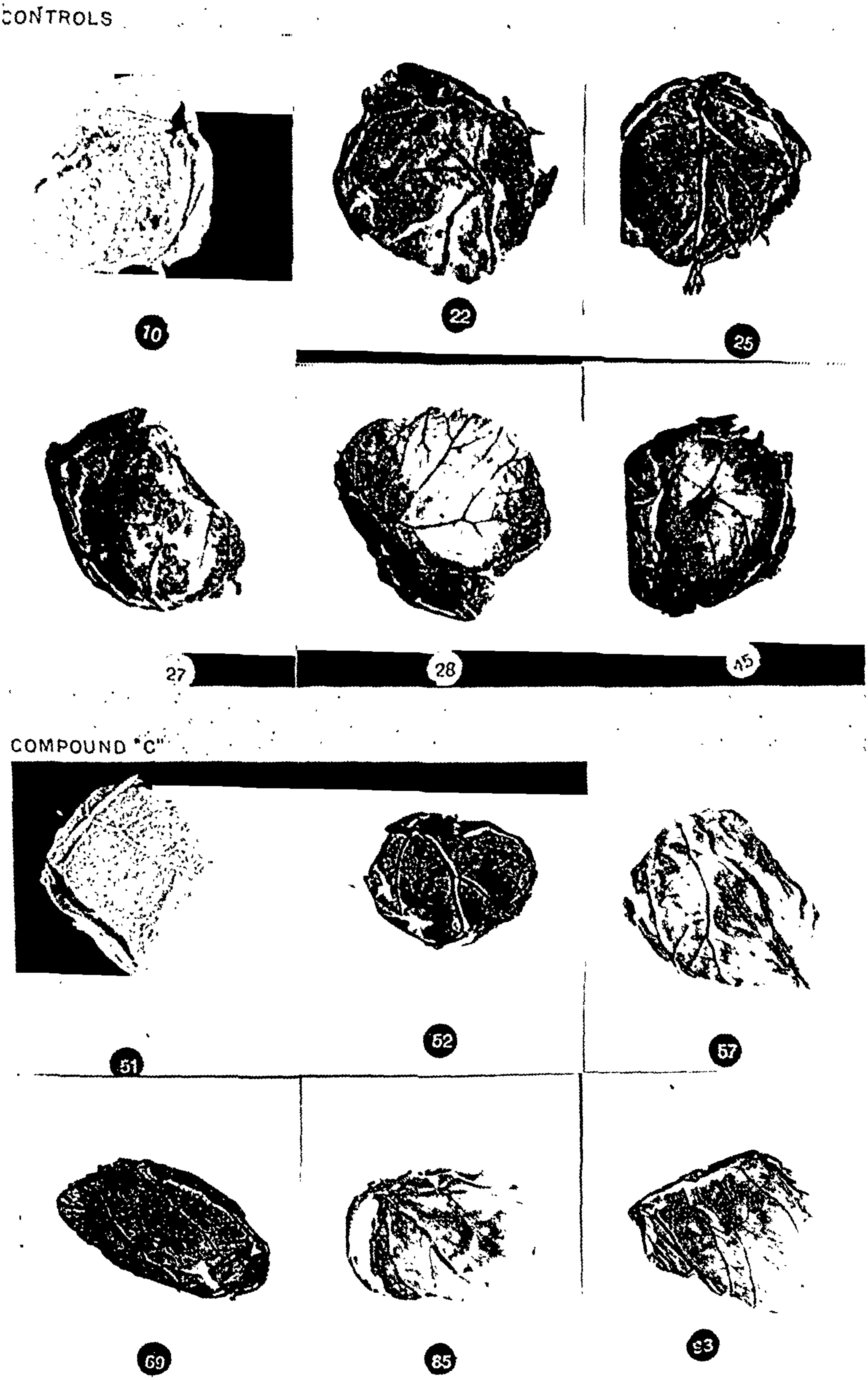


PLATE 1. Chorio-allantoic membranes inoculated with 1 mg. of tubercle bacilli (A 27)
Above—Controls—inoculated with untreated suspension.
Below—Compound "C"—inoculated with suspension exposed to sodium-3-amyl-cyclopentane carboxylate for twenty-four hours.

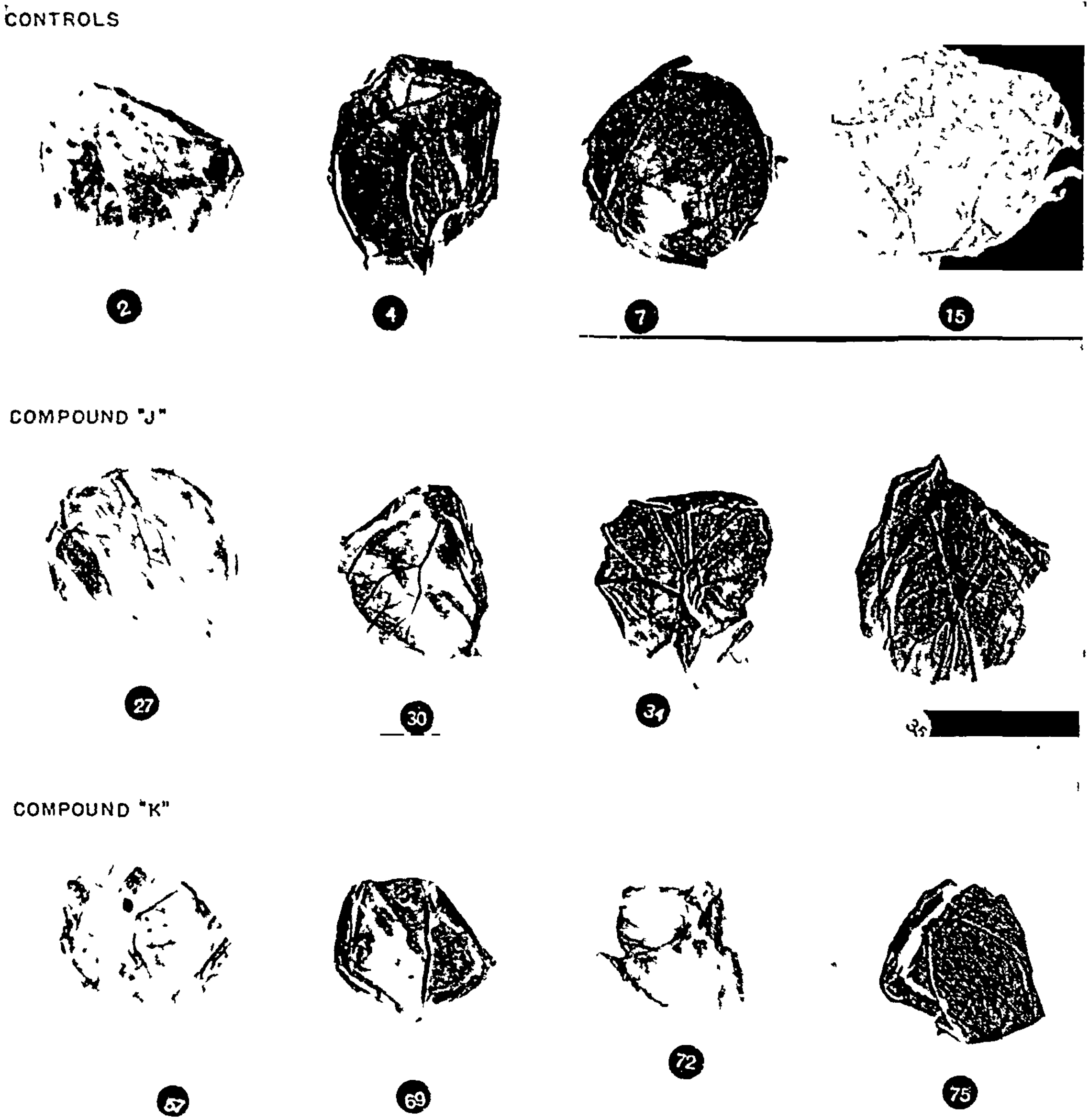


PLATE 2. Chorio-allantoic membranes inoculated with 1 mg. of tubercle bacilli (A 27)
Top row—Controls—inoculated with untreated suspension.

Middle row—Compound "J"—inoculated with suspension exposed to sodium-4-cyclohexylcyclohexane carboxylate for twenty-four hours.

Bottom row—Compound "K"—similar experiments using sodium-3-cyclopentylcyclopentylacetate.

taining sodium-3-amyl-cyclopentane carboxylate ("C") (plates 1 and 2). The inocula containing compounds "J", "C" or "L" produced in some of the membranes edematous vesiculated lesions. These were most numerous in the experiments in which compound "J" (sodium-4-cyclohexylcyclohexane carboxylate) was used. These translucent vesicles in microscopic section were found to be filled with fluid. Eosinophils and monocytes were present, with bacilli both in the fluid and within the cytoplasm of the cells. Frequently in the same membrane a few typical tubercles were found in early stages of development. Membranes inoculated with suspensions containing sodium-3-amyl-cyclopentane carboxylate produced similar results. Only a few membranes inoculated with the "L" compound showed vesicular lesions and none were observed when the "K" compound was used. No vesiculated lesions appeared in any membranes of the control groups, all of which had numerous typical tubercles.

In table 3 there is also given an analysis of the tuberculous development as determined by microscopic examination of the membranes. The degree of development of the tubercle has arbitrarily been evaluated from 0 to 4, 4 representing the typical compact necrotic and caseating tubercle. In the control series all stages of tubercle development may be found from small aggregates of monocytes, surrounding clumps of bacilli, to the fully developed tubercle. By contrast the membranes inoculated with drug-bacilliary suspension showed few fully developed tubercles, the lesions consisting for the most part of aggregates of eosinophils and monocytes.

CONCLUSIONS

It has been shown that certain cyclopentyl compounds chemically related to chaulmoogric acid and certain cyclohexyl alicyclic acids produced marked inhibition in growth of tubercle bacilli of the A27 strain in both Kirchner's medium and Difco beef bouillon. Four of these compounds, sodium-3-amyl-cyclopentane carboxylate, sodium-3-cyclohexylcyclopentylacetate, sodium-3-cyclopentyl-cyclopentylacetate and sodium-4-cyclohexylcyclohexane carboxylate, were found to be highly tuberculostatic. Under the same experimental conditions the sodium salt of chaulmoogric acid was considerably less effective.

Judged by the incidence and extent of tubercle formation of infected chorio-allantoic membranes of the chick embryo, the virulence of suspensions of bacilli exposed to the action of 0.5 mg. of these drugs in 0.2 cc. of suspension for twenty-four hours was greatly attenuated as compared with that of control suspensions in physiological saline. The marked activity of these four compounds in relatively low doses suggests that further studies in other experimental animals would be profitable.

CONCLUSIONES

Se ha demostrado que ciertos compuestos ciclopentílicos químicamente afines del ácido chalmúgrico y ciertos ácidos ciclohexílicos alicíclicos producen una inhibición pronunciada en la proliferación de la cepa A 27 tanto en el medio de Kirchner como en el caldo de res Difco. Cuatro de esos compuestos, el

3 amil-ciclopentano carboxilato sódico, el 3 ciclohexilciclopentilacetato sódico, el 3 ciclopentilciclopentil acetato sódico y el 4 ciclohexilciclohexano carboxilato sódico resultaron ser muy tubérculoestáticos. En las mismas condiciones de experimentación la sal sódica del ácido chalmúgrico resultó considerablemente menos eficaz.

A juzgar por la incidencia y extensión de tubercúlogenia de las membranas corio-alantóicas infectadas del embrión de pollo, la virulencia de las suspensiones bacilares expuestas a la acción de 0.5 mg. de estas drogas en 0.2 cc. de suspensión durante 24 horas se atenuó considerablemente comparada con la de las suspensiones testigos en sueros fisiológicos. La marcada actividad de estos 4 compuestos a dosis relativamente bajas indica que resultarían provechosos nuevos estudios en otros animales de experimentación.

REFERENCES

(1) Walker, E. L., and Sweeney, M. A.: The chemotherapeutics of the chaulmoogric acid series and other fatty acids in leprosy and tuberculosis, J. Infect. Dis., 1920, *26*, 238.

(2) Walker, E. L.: Progress report on the investigation of the chemotherapeutics of chaulmoogric acids in tuberculosis, Tr. Nat. Tuberc. A., 1921, p. 392.

(3) Walker, E. L., McArthur, C. G., and Sweeney, M. A.: Second progress report on the investigation of the chemotherapeutics of chaulmoogra oil and its derivatives in leprosy and experimental tuberculosis, Tr. Nat. Tuberc. A., 1922, p. 553.

(4) Voegtlin, C., Smith, M. I., and Johnson, J. M.: Therapeutic value of chaulmoogra oil and its derivatives in experimental tuberculosis, J. A. M. A., 1921, *77*, 1017.

(5) Wagner-Jauregg, Th.: Experimental chemotherapy of tuberculosis with chaulmoogra and hydnocarpus preparations, Ber. ges. Physiol., 1943, *132*, 400.

(6) Prigge, R.: Experimental studies on the chemotherapy of tuberculosis, Klin. Wchnschr., 1940, *2*, 1273.

(7) Prigge, R.: Experimental studies on the chemotherapy of tuberculosis, Klin. Wchnschr., 1941, *2*, 633.

(8) Arnold, H. E. Helmert, Mobus, Th., Prigge, R., Ransen, H., and Wagner-Jauregg, Th.: Long chain sulfonamides and their therapeutic properties, Ber. Deutsche Chem. Ges., 1942, *75*, 369.

(9) Emmart, E. W., and Smith, M. I.: The growth and effects of the tubercle bacillus on the chorio-allantoic membrane of the chick embryo, Pub. Health Rep., 1941, *56*, 1277.

(10) Emmart, E. W., and Smith, M. I.: The attenuating effect of promin on virulence of the tubercle bacillus, Proc. Soc. Exper. Biol. & Med., 1942, *51*, 320.

(11) Emmart, E. W., and Smith, M. I.: The chorio-allantoic membrane of the chick embryo as a medium for testing the virulence of tubercle bacilli, Am. Rev. Tuberc., 1943, *47*, 426.

AMERICAN TRUDEAU SOCIETY

Report of the Committee on Therapy

June, 1945

Dr. H. Corwin Hinshaw, *Chairman*

Dr. André Cournand	Dr. John C. Jones
Dr. John N. Hayes	Dr. Theodore N. Rafferty
Dr. Kirby S. Howlett, Jr.	Dr. John D. Steele

The Committee on Therapy has concluded a questionnaire project to acquire information regarding trends of thought concerning the place of pneumoperitoneum as a collapse measure in treatment of pulmonary tuberculosis in the larger sanatoria of the United States. The replies received were much more generous than could have been anticipated in such difficult times and concerning a topic that is frequently considered to be of minor importance. The institutions responding have an aggregate total of over 25,000 occupied beds. Approximately 1,600 cases with pneumoperitoneum were reported. While no effort was made to determine efficacy of the procedure, a definite effort was made to learn of the potential risks of artificial pneumoperitoneum. It was specifically indicated that the results would not be published, but mimeographed summaries are available through the New York office of the American Trudeau Society.

Perhaps the most important function of the pneumoperitoneum questionnaire was a "trial balloon" to learn if this informal method of obtaining and distributing information could serve a useful purpose and would be favored by sanatorium physicians. Over 90 per cent of individuals replying expressed approval of the method. Many suggestions were received for further studies.

The Committee held a two-day meeting on February 1 and 2, 1945, in Chicago. The following subjects were among those discussed:

1. *Bed-rest therapy:* It was agreed that special efforts should be made to make it clear to physicians that current discussions on "abuse of bed-rest" in treatment of some other diseases do not apply to the treatment of tuberculosis.

2. *Management of oleothorax:* The Committee recommended publication of the following statement for guidance in care of patients with oleothorax: "It is recommended that for the maintenance of oleothorax clinical review, roentgenographic examination, exploration for presence of exudate and determinations of pressure within the cavity should be frequently carried out. The interval between checks should be brief at first and gradually be extended to a period of not in excess of three months after the oleothorax becomes stabilized."

3. *Definition of negative sputum in evaluation of therapy:* The Committee met jointly with the Committee on Evaluation of Laboratory procedures for exploration of this problem and after extensive discussion concluded that more precise and uniform bacteriological standards would be desirable additions to the other criteria utilized in classification of the recovery phases of tuberculosis.

4. *Clinical applications of chemotherapy:* The present status of some controlled studies of chemotherapy of clinical tuberculosis was reviewed and the definite trend toward diminishing enthusiasm for promin, diasone and promizole was noted. The present status of streptomycin in treatment of experimental tuberculosis of guinea pigs was briefly reviewed.

The Committee has recognized the increasing importance of tests of pulmonary function in calculating the risks of contemplated permanent collapse therapy or pulmonary resection and in measuring the physiological effects of surgical procedures at various stages of the postoperative period. As a result of extended discussions during the past two years the Committee requested one of its members, Dr. André Cournand, to undertake the task of securing recommendations from several investigators and of compiling these in a manner to serve the physician and surgeon in practical application of these tests to the more frequently encountered problems in surgical treatment of pulmonary tuberculosis.

Generous replies were received from the following physicians: Dr. John LaDue, Dr. Max Pinner, Dr. George Wright and Dr. Frederick Warring. The Committee wishes to express their gratitude to them and to Dr. André Cournand, who has prepared the following report in an effort to correlate his own views with those expressed by the above mentioned advisers.

TESTS OF PULMONARY FUNCTION IN THEIR RELATION TO THE TREATMENT OF CHRONIC PULMONARY TUBERCULOSIS

Studies of pulmonary function are of practical interest in two groups of patients with chronic pulmonary tuberculosis:

Group I comprises patients in whom collapse therapy or pulmonary resection is indicated. In this group, tests of pulmonary function may be used chiefly (*a*) to detect poor surgical risks, (*b*) to help predict difficulties during the immediate postoperative period and the degree of disability to be expected after surgery has been completed, and (*c*) to decide whether one type of treatment should be substituted for another. They should be viewed as valuable information to be discussed along with other information obtained by a complete clinical survey of the case.

As a rule, in young individuals, with single cavities and no evidence of homo- or contralateral scattered bronchogenic spread, tests of pulmonary function may be dispensed with. A history of repeated hemoptysis, which may lead to fine nodular and disseminated fibrosis and extensive emphysema of the better lung, sometimes difficult to recognize on X-ray films, constitutes the only exception to this rule and one of the main indications for complete study of the pulmonary function including the six sets of measurements.

Group II comprises patients who have been recently subjected to a major surgical procedure such as thoracoplasty, lobectomy or pneumonectomy. In this group the following tests may be used to advantage: (*a*) Immediately after surgery measurement of the arterial blood oxyhemoglobin saturation will help decide whether latent anoxia is present; cyanosis is a late sign of an anoxic state,

especially after loss of blood and in anemic persons; it is therefore of little practical value in dealing with oxygen therapy. (b) Following lobectomy and pneumonectomy, measurement of maximal breathing capacity and measurement of lung volume (tests 1 and 3 below) will be of importance in detecting early distention of the homolateral lobes or contralateral lung. They should be repeated during the first few months after lung resection, with a view to helping decide whether to collapse the chest wall partially or totally on the side of the lung resection as a preventive measure against further pulmonary distention and possible development of emphysema.

The tests recommended may be listed and indexed as follows:

Test 1: Measurement of the maximum breathing capacity (maximum minute ventilation).

Test 2: Separate measurements of the ventilation and oxygen intake of each lung (bronchospirometry).

Test 3: Measurement of the total lung volume, including residual air.

Test 4: Measurement of the arterial blood oxyhemoglobin saturation at rest and following exercise.

Test 5: Measurement of the ventilation and of rate of oxygen intake at rest, during and following a standard type of exercise.

Test 6: Fluoroscopic observation to observe movements of the thoracic cage and diaphragms.

Tests 1 and 2 constitute the minimum required in both young and aged groups with previous history of collapse therapy, bilateral disease, adhesive pleuritis or of serofibrinous pleurisy and in the presence of bronchial lesions. Test 1 gives information regarding the available breathing reserve; although there is no fast rule, experience has shown that, when the maximum breathing capacity is below 40 liters per minute in males and 35 liters per minute in females, the immediate postoperative period may be stormy and permanent disability in the form of dyspnea with minimal exertion, or even at rest, may develop. Test 2 may be valuable in helping (a) decide whether to be conservative in rib resection, (b) choose between thoracoplasty, partial or total lung resection. If oxygen intake is still large and proportional to the ventilation on the side to be operated upon, attempt should be made to restrict surgical procedure to the minimum compatible with good therapeutic result; on the contrary, a much reduced oxygen intake with still a large ventilation should be an inducement to an extensive collapse of the chest wall or to total lung resection. Tests 1, 2, 3, 4 and 5 should be used in the older age group when dyspnea is an important symptom and if there is suggestion that chronic pulmonary emphysema is a complicating factor. Whenever a bronchial lesion is suspected, tests 1 and 3 are of real diagnostic value in showing (a) a much larger reduction in Maximum Breathing Capacity than in Vital Capacity, (b) discrepancies in successive measurements of residual air volume.

In forwarding these recommendations to members of the Society, the Committee should insist upon the importance of (*1*) a good technique in obtaining the

data, (2) a thorough understanding of the general concept of pulmonary function on the part of those interpreting the measurements. It should be emphasized, too, that, great progress having been made in the field of applied respiratory physiology during the war, the suggestions made here will certainly be supplemented and revised in the not too distant future when restrictions on scientific information are lifted.

AMERICAN TRUDEAU SOCIETY

Report of the Committee on Clinic Procedure

June, 1945

Dr. Herbert R. Edwards, *Chairman*

Dr. R. Alec Brown — Dr. Herbert L. Mantz

Dr. Edward S. Kupka — Dr. Paul P. McCain

Dr. Paul S. Phelps

The Committee on Clinic Procedure held a meeting on January 30, 1945, in Chicago. Committee members present were Dr. Herbert R. Edwards, Chairman, Dr. R. Alec Brown, Dr. Edward Kupka, Dr. Paul P. McCain and Dr. Paul S. Phelps.

The purpose of the meeting was to discuss the revision of the *Tuberculosis Clinic Manual*, published by the National Tuberculosis Association in 1938, the task of revision having been assigned to the Committee.

The various chapters of the manual were assigned to Committee members for revision. Each chapter was thoroughly discussed at the meeting so that the Committee member assigned a particular chapter would have the benefit of the other Committee members' ideas on the subject. It was decided that each Committee member should have sufficient copies made of his revisions, so that a copy could be sent to the other members for comment. All suggestions for further changes were to be in the exact wording desired. Doctor Edwards agreed to assemble the revisions before submitting the material to a medical editor for review, and the Committee gave him the power to make all necessary final decisions. The Committee also recommended that the typography of the manual be improved and that the name be changed to *Chest Clinic Manual.*

Since the meeting, the Committee members have been working on the chapters assigned to them and revisions are being sent around for comment. It is expected that the manuscript will be ready for publication the latter part of the year.

AMERICAN TRUDEAU SOCIETY

Report of the Medical Advisory Committee on Health Education

Dr. H. McLeod Riggins, *Chairman*

Dr. Charles P. Cake   Dr. Kirby S. Howlett, Jr.   Dr. B. Thomas McMahon

The Medical Advisory Committee on Health Education did not meet during the year, but carried on its work by correspondence. Through the courtesy of Doctor Lyght, Doctor Cake and Doctor Riggins met with the Advisory Committee on Health Education of the N.C.T.S. on February 1, 1945. The Chairman made a short report of the activities of the Medical Advisory Committee during 1944. He reviewed very briefly the scope and functions of the Medical Advisory Committee and pointed out the necessity for greater clarification of the Committee's function particularly as regards the review of monographs sponsored by the N.T.A., but written by recognized authorities on special subjects in the field of tuberculosis. It is the consensus of the Medical Advisory Committee that more explicit clarification of its functions is advisable, particularly as regards the review of monographs or texts sponsored by the N.T.A.

During the year, the Committee reviewed the following manuscripts:

Why Does TB Run in the Family
Teaching Unit on Tuberculosis Control Designed for High Schools
Motion picture script *Lease on Life*
Doctor Aitken's manuscript *Care and Treatment of the Tuberculous*
Manuscripts of 1945 Christmas Seal School Programs
Tuberculosis through the Teens
Industrial Bulletin Board Posters
Your Baby

Dr. B. Thomas McMahon of Denver has recently been made a member of the Committee.

The observations and suggestions of the various members of the Committee have been received reasonably promptly in most instances, and they, with the Chairman's comments, have been communicated to the Director (of the Department) of Health Education. As has been the custom in previous years, the members of the Committee sent a carbon copy of their comments and suggestions to the Chairman. In certain instances the Chairman has not only forwarded a summary of the Committee's report to the National Office, but has also sent carbon copies of the members' comments.

NOTICE

Prof. Dr. Fernando D. Gómez, Director, announces that the fourth post-graduate course, Theoretical and Practical Aspects of the Treatment of Pulmonary Tuberculosis, will be given in the Instituto de Tisiologia "Prof. Juan B. Morelli," Montevideo, Uruguay, March 18 to 30, 1946.

CHEST PHOTOROENTGENOGRAPHY IN ARMY PHYSICAL EXAMINATIONS

A Review of 40,283 Chest Photoroentgenograms at the Buffalo Recruiting and Induction Station[1]

ISRAEL A. SCHILLER[2]

INTRODUCTION

Radiography of the chest as part of the Army physical examination for induction constitutes a mass survey for tuberculosis of the male population of military age. It may be estimated that, in order to raise an Army of 7½ million men, approximately 10 million must be examined by the Army Medical Corps. Thus, roughly 7.5 per cent of our total population will be given the benefit of a chest roentgenogram. A systematic screening of the apparently healthy population has never before been undertaken on such an enormous scale.

The knowledge gained from this program will serve to evaluate our progress in the fight against pulmonary tuberculosis and will uncover the reservoirs where the disease has resisted efforts at control, and which serve as foci for its dissemination. The immediate benefits of this project will be experienced in every community through the discovery of cases of previously undiagnosed tuberculosis.

This report of the findings in 40,283 chest photoroentgenograms is presented as a small part of this vast survey.

MATERIAL

The examinations which form the subject of this report were made at the Buffalo Recruiting and Induction Station during the six-month period from July 1 to December 31, 1942. The majority of the men examined were derived from an area embracing six counties in Northwestern New York State with a population of 1,225,794. This population is chiefly urban, the greater part of it being concentrated in the Buffalo-Niagara Falls Metropolitan District which has a population of 857,719.

The 40,283 men examined consisted of four groups: (*1*) Selective Service Registrants; (*2*) Applicants for Enlistment; (*3*) Applicants for Commission; (*4*) Applicants for Aviation Cadet Training. The size and the age limits of each group examined are summarized in table 1. Exact data as to the distribution within the upper and lower age limits for each group are not available, but in general the Selective Service Registrants contained more men in the higher age brackets than the Applicants for Enlistment. The Applicants for Commission were, for the most part, between 30 and 45 years of age, with less scatter in the younger age groups than the preceding two subdivisions. This was, on

[1] A unit of the Northwestern New York Recruiting District, Second Service Command.

[2] Major, Medical Corps, Army of the United States. Address: 1369 East 19th Street, Brooklyn, New York.

the average, the oldest, as well as the smallest group examined. In addition, this group contained a substantial number of physicians and dentists. The youngest category was the Aviation Cadet Applicants, ranging in years between 18 and 27. The latter was a selected group, since all Aviation Applicants had passed a mental aptitude test prior to physical examination.

TABLE 1

Size and age limits of groups examined

	NUMBER EXAMINED	PER CENT	AGE LIMITS
Selective service registrants	29,778*	73.9*	18–45
Applicants for enlistment	7,643	19.0	18–45
Applicants for commission	784	1.9	21–50
Applicants for aviation cadet training	2,078	5.2	18–27
Total	40,283	100.0	18–50

* Included in this number were 961 colored men who formed 3.2 per cent of the Selective Service Registrants and 2.4 per cent of the total examined.

METHOD

The chest of every man was X-rayed by the photoroentgen technique, a pair of stereoscopic exposures being made in each case. The two exposures were made during one inspiration with a vertical shift of the tube and film. The resulting photoroentgenogram consisted of two images, each approximately 4″ x 5″, one above the other, on a film 4″ x 10″ in size. The films were viewed while wet through an ortho-stereoscope which magnified the image three times and permitted tri-dimensional visualization. In doubtful cases, or where closer scrutiny was required, conventional 14″ x 17″ chest films were made. The details of procedure and equipment have been described more fully elsewhere (1, 2).

In cases where the radiographic findings were cause for rejection, the registrant or applicant was interviewed by the roentgenologist. A brief history was obtained and the reason for rejection explained, with special emphasis on the importance of seeking prompt medical care. In addition, the names and addresses of rejected individuals, together with the diagnosis, were submitted daily to the New York State Department of Health.

CRITERIA FOR REJECTION

Under present Army Regulations, men who show radiographic evidence of the reinfection or adult type of tuberculosis, involving an area of the lung field larger than 5 square centimeters on the standard 14″ x 17″ film are rejected regardless of the activity of the disease. Where the lesion shows definite evidence of inactivity and is not greater in extent than 5 square centimeters, acceptance is deferred for a length of time sufficient to demonstrate the stability of the process, six months being regarded as the minimum period to satisfy this requirement. Similarly, persons with active or unstable primary tuberculosis are rejectable. Men with residua of healed primary tuberculosis are considered acceptable provided the number of calcified foci is not excessive.

Among the chronic nontuberculous pulmonary diseases which call for rejection, bronchiectasis, wide-spread pulmonary fibrosis and extensive adhesive pleurisy are probably the most important from the point of view of the Army examiner. Pleural effusion, neoplastic disease, mediastinal or hilar adenopathy, and eventration of the diaphragm also bar the candidate from acceptance for military service.

Men with temporarily disabling conditions, such as pneumonia or spontaneous nontuberculous pneumothorax, are deferred for periods of from one to three months. Similarly, when a lesion is suspected, or if further observation is required before a definite diagnosis can be made, the registrant or volunteer may be deferred temporarily at the discretion of the examiner. Such temporary deferment is considered especially advisable in cases of recent "idiopathic" pleural effusion.

It is evident that many cases will be found suitable for temporary deferment rather than for outright rejection. The frequent use of the "temporarily deferred" classification is therefore not to be regarded merely as a postponement of the ultimate decision, but as a recognition of the importance of the time element in arriving at a sound estimate of fitness for military service.

RESULTS

The results of this study, in general terms, are summarized in table 2. Of the total number examined, 856 men, or 2.12 per cent, were found to be unfit for military service, temporarily or permanently, because of pulmonary disease disease as revealed in the photoroentgenogram. Pulmonary tuberculosis was the cause of rejection in approximately three-quarters of these, nontuberculous pulmonary diseases accounting for only one-quarter of the rejections. Specifically, there were 632 rejections for tuberculosis, or 1.57 per cent of the entire group examined, compared with 224, or 0.55 per cent, for other pulmonary conditions.

The total of 856 cases rejected because of pulmonary disease may be divided also into 510 (1.27 per cent) permanently disqualified and 346 (0.85 per cent) temporarily deferred. Almost half of the rejections (40 per cent) therefore were temporary, for periods of from one to six months, and subject to reëxamination at a later date. Whether temporary or permanent, tuberculosis was responsible for roughly three-fourths of the cases in each category. Thus, of the 632 cases rejected because of tuberculosis, 374, or 0.93 per cent, were rejected permanently, while 258, or 0.64 per cent, were deferred temporarily; of the 224 nontuberculous cases, 136, or 0.34 per cent, were rejected permanently and 88, or 0.21 per cent, deferred temporarily.

Tuberculosis: An examination of the figures for tuberculosis (table 2), however, reveals considerable variation among the different classes. Selective Service Registrants, the largest group, showed a rejection rate for tuberculosis of 1.77 per cent. Applicants for training as Aviation Cadets yielded the lowest rate—0.72 per cent, while those examined for the commissioned grades gave the highest rate—2.55 per cent. The latter two classes of applicants also repre-

sented the extremes with regard to age, the Air Corps aspirants being limited to men under 28, while the applicants for commissions were preponderantly over 30 years of age. The latter, numbering only 784 men, constituted too small a group to permit reliable conclusions as to the prevalence of tuberculosis in the older age brackets, but this trend toward an increasing prevalence of tuberculosis with advancing years has been noted in other surveys (2, 3).

The applicants for voluntary enlistment, the second largest group in the series studied, showed a rejection rate for tuberculosis of 0.93 per cent, only slightly higher than that of the aviation applicants and substantially lower than that of the Selective Service Registrants. These volunteers were not only generally

TABLE 2

Analysis of 856 cases permanently or temporarily rejected because of pulmonary disease

GROUP AND NUMBER	PERMANENTLY REJECTED		TEMPORARILY REJECTED		TOTAL X-RAY REJECTS		PULMONARY TUBERCULOSIS						OTHER PULMONARY					
							Permanent		Temporary		Total		Permanent		Temporary		Total	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Selective service registrants, 29,778	435	1.46	289	0.97	724	2.43	312	1.05	214	0.72	526	1.77	123	0.41	75	0.25	198	0.66
Applicants for enlistment, 7,643	43	0.56	46	0.60	89	1.16	35	0.46	36	0.47	71	0.93	8	0.10	10	0.13	18	0.23
Applicants for commission, 784	16	2.04	4	0.51	20	2.55	16	2.04	4	0.51	20	2.55	0	0	0	0	0	0
Applicants for aviation cadet training, 2,078	16	0.77	7	0.34	23	1.11	11	0.53	4	0.19	15	0.72	5	0.24	3	0.15	8	0.39
Total 40,283	510	1.27	346	0.85	856	2.12	374	0.93	258	0.64	632	1.57	136	0.34	88	0.21	224	0.55

younger than the Selective Service Registrants, but most of them, like the applicants for aviation training, had some special educational or technical qualifications. This superiority may reflect a better social and economic background and be an additional factor in accounting for their lower rate of rejection for tuberculosis.

Colored registrants, numbering 961 men, formed only a small proportion (3.2 per cent) of the men derived through Selective Service. Their rate of rejection for tuberculosis was the same as that of the white registrants—1.77 per cent, and their rate for other pulmonary diseases also showed no significant difference—0.73 per cent, as compared with 0.66 per cent for the white regis-

trants. Because of the small size of the Negro component, however, no far-reaching conclusions can be drawn from these figures.

TABLE 3

Analysis of 374 cases permanently rejected because of pulmonary tuberculosis

GROUP	NUMBER EXAMINED	PERMANENTLY REJECTED BECAUSE OF TUBERCULOSIS		ACTIVE TUBERCULOSIS				ARRESTED TUBERCULOSIS	PRIMARY TUBERCULOSIS		
		Number	Per cent	Minimal	Moderately advanced	Far advanced	Total	Arrested	Unstable	Healed	Total Primary tuberculosis
Selective service registrants....	29,778	312	1.05	58	60	10	128	164	2	18	20
Applicants for enlistment....	7,643	35	0.46	6	7	0	13	15	0	7	7
Applicants for commission...	784	16	2.04	3	0	0	3	12	0	1	1
Applicants for aviation cadet training.......	2,078	11	0.53	5	2	0	7	4	0	0	0
Total.........	40,283	374	0.93	72	69	10	151	195	2	26	28

TABLE 4

Analysis of 258 cases temporarily deferred because of pulmonary tuberculosis

GROUP	NUMBER EXAMINED	TEMPORARILY DEFERRED BECAUSE OF TUBERCULOSIS		ACTIVITY UNDETERMINED				ARRESTED		PRIMARY TUBERCULOSIS				SUSPICIOUS OF TUBERCULOSIS	
		Number	Per cent	Probably active	Probably arrested	Total	Per cent	Number	Per cent	Unstable	Healed	Total	Per cent	Number	Per cent
Selective service registrants......	29,778	214	0.72	27	45	72	0.24	131	0.44	5	4	9	0.03	2	<0.01
Applicants for enlistment........	7,643	36	0.47	5	5	10	0.13	20	0.26	3	0	3	0.04	3	0.04
Applicants for commission.........	784	4	0.51	0	0	0	0	4	0.51	0	0	0	0	0	0
Applicants for aviation cadet training............	2,078	4	0.19	0	1	1	0.05	2	0.09	0	0	0	0	1	0.05
Total..........	40,283	258	0.64	32	51	83	0.21	157	0.39	8	4	12	0.03	6	0.01

Examining the cases attributable to tuberculosis with regard to the stage and activity of the disease (table 3) we note that, of 374 permanently rejected for this cause, 195 were classed as arrested, or not clinically significant, and 151

as active. Twenty-eight cases were of the primary type—2 unstable and 26 healed.

The cases temporarily rejected because of tuberculosis are analyzed in table 4. It will be recalled from the discussion under Criteria for Rejection that cases of reinfection type tuberculosis, to be eligible for temporary deferment, must be limited in extent to an area not exceeding 5 square centimeters on the 14" x 17" film, and show evidences of arrest of the lesion. However, in order to avoid too great reliance on the roentgenogram alone in estimating the activity of tuberculous lesions, all cases of minimal tuberculosis which conformed to the stated dimensions and were not frankly active radiographically or clinically were deferred temporarily. In these cases the ultimate decision as to the activity of the process was to be made after six or more months of observation. This policy resulted in the temporary deferment not only of cases which seemed definitely arrested, but also of cases of undetermined activity, some of which were probably inactive and others probably active, judging from the available evidence.

Referring to table 4, we note that, of 258 cases temporarily deferred because of tuberculosis, 157, or approximately three-fifths, were considered arrested, while 83 were of doubtful activity. Subdividing the doubtful cases, as described above, we find that 51 were considered "probably arrested," and 32 "probably active." Twelve cases of the primary type of tuberculosis, and 6 cases in which the existence of a lesion, possibly tuberculous, was suspected, complete the total of those temporarily deferred by reason of tuberculosis. It is safe to assume that the majority of the men in this category would prove acceptable after six months of observation.

The necessarily arbitrary separation of the cases of tuberculosis into permanently and temporarily rejected categories does not give a complete picture of the disease as seen by the Army roentgenologist. For this reason, tables 3 and 4 have been combined to form table 5, which analyzes all of the 632 cases rejected because of pulmonary tuberculosis, by stage and activity of the disease. The cases listed in table 4 as "probably active" have been included under "minimal active," while the "probably arrested" and "arrested" headings of table 4 have been incorporated into the "arrested" column in table 5.

The composite tabulation shows 183 cases (0.45 per cent) of active, or clinically significant tuberculosis, as compared with 403 (1.00 per cent) arrested. The active cases considered by stage of the disease were distributed as follows: 104, or 56.8 per cent, were minimal; 69, or 37.7 per cent, were moderately advanced; and 10, or 5.4 per cent, were far advanced. All of the far advanced cases occurred among the Selective Service Registrants. There were also 40 cases of the primary type of tuberculosis, either unstable or healed

The ratio of active to arrested cases for the entire group was 1:2.2. This ratio held equally well for the Selective Service Registrants and Applicants for Enlistment, who together constituted over 90 per cent of the men examined. In this regard, however, the two smaller groups differed sharply, the youngest applicants (Aviation Cadets) presenting an equal number of active and arrested

cases while the oldest (Applicants for Commission) showed only 3 active cases as compared with 16 arrested. Thus, although the older men showed the highest rate of rejection because of tuberculosis (2.55 per cent), this could be attributed to the greater prevalence of arrested disease among them.

Nontuberculous cases: Referring again to table 2, it will be noted that 224 men (0.55 per cent) were rejected because of nontuberculous pulmonary disease, of whom 136 (0.34 per cent) were permanently excluded from military service and 88 (0.21 per cent) only temporarily disqualified. The ratio of temporary to permanent rejections here is approximately that found for tuberculosis, namely 2:3.

In the field of nontuberculous disease, Selective Service Registrants showed the highest rate of rejection—0.66 per cent, while those applying for commissions

TABLE 5

Analysis of 632 cases rejected because of pulmonary tuberculosis (composite of tables 3 and 4)

GROUP	NUMBER EXAMINED	REJECTED BECAUSE OF TUBERCULOSIS		ACTIVE TUBERCULOSIS					ARRESTED TUBERCULOSIS		PRIMARY TUBERCULOSIS		SUSPICIOUS OF TUBERCULOSIS	
		Number	Per cent	Minimal	Moderately advanced	Far advanced	Total	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Selective service registrants....	29,778	526	1.77	85	60	10	155	0.52	340	1.14	29	0.10	2	<0.01
Applicants for enlistment....	7,643	71	0.93	11	7	0	18	0.23	40	0.52	10	0.13	3	0.04
Applicants for commission...	784	20	2.55	3	0	0	3	0.38	16	2.04	1	0.13	0	0
Applicants for aviation cadet training......	2,078	15	0.72	5	2	0	7	0.34	7	0.34	0	0	1	0.05
Total.........	40,285	632	1.57	104	69	10	183	0.45	403	1.00	40	0.10	6	0.01

lost none on this score. The other two classes of applicants had comparable rates—0.23 per cent of those who sought to enlist and 0.39 per cent of those who sought flight training being excluded on this count.

Table 6 lists the diseases encountered other than tuberculosis, and the number of rejections attributable to each. Bronchiectasis, with 51 cases, was the most frequent cause of rejection in this group. The diagnosis was based on the rather characteristic infiltration in the roentgenogram together with one or more confirmatory clinical features, such as a history of chronic cough with expectoration, clubbing of the fingers, previous bronchography, or physical signs commonly associated with this disease. Thirteen of these cases were deferred temporarily to test the persistence of the radiographic changes. Several cases, in which bronchiectasis was the most probable underlying etiological factor, were diagnosed as "pneumonitis" on the basis of the X-ray findings and rejected tempo-

rarily. Undoubtedly some of the cases rejected because of fibrosis would also show bronchiectatic changes on bronchography, but these were classed as instances of pulmonary fibrosis, in accordance with their predominant radiographic characteristic. In a large number of cases reported from the Southern New York Recruiting District (2), the diagnosis of bronchiectasis, made on the same criteria as employed in this series, was later confirmed by bronchography in 54 of 57 cases. While the number of cases of bronchiectasis in the present

TABLE 6

Analysis of 224 cases permanently or temporarily rejected because of pulmonary diseases other than tuberculosis

Bronchiectasis		51
Pneumonitis		45
Diseases of the pleura		44
Adhesive pleurisy and thickened pleura	31	
Pleural effusion	5	
Recent pleural effusion	4	
Acute fibrinous pleurisy	2	
Spontaneous pneumothorax	2	
Pulmonary fibrosis and emphysema		32
Hilar and mediastinal adenopathy		16
Pneumonoconiosis		11
Silico-tuberculosis	4	
Eventration of diaphragm		8
Left leaf	4	
Right leaf	3	
Bilateral	1	
Mediastinal neoplasm		4
Healed tuberculous cervical adenitis		3
Substernal goitre with tracheal compression		2
Neoplasm of rib		2
Neoplasm of scapula		1
Calcified pulmonary mass		1
Cystic disease of lungs		1
Chronic bronchitis		1
Aortic aneurysm		1
Coarctation of the aorta		1
Total		224

series is high in comparison with the findings in the report cited, it is believed that the estimate is conservative.

The disease group occurring next in order of frequency is listed as "pneumonitis," which is admittedly a nonspecific and inclusive designation. The 45 cases classed under this heading comprise a variety of diseases, some of them chronic or secondary to other causative factors. As mentioned above, several were probably the result of underlying bronchiectasis, while one at least was a case of chronic lung abscess. Here, too, were included the bronchopneumonias

and other transient pulmonary infiltrations, as well as the one case of frank lobar pneumonia encountered in the series. It is possible that some of the cases thus listed would prove to be tuberculous in origin. Because many were undoubtedly of transient nature, while others were of uncertain etiology, 44 of the 45 cases loosely grouped as "pneumonitis" were deferred for short periods of time, to be reëxamined later.

Diseases of the pleura accounted for 44 rejections, of which adhesive pleurisy and thickening of the pleura together were responsible for 31. There were also 5 cases of pleural effusion (one encapsulated and one interlobar) and 4 cases recently recovered of pleural effusion which were deferred temporarily. In all of these cases the history was suggestive of the so-called "idiopathic" type of pleural effusion. Acute fibrinous pleurisy and spontaneous pneumothorax complete the tally of diseases of the pleura, each with 2 cases temporarily deferred. Although this group of cases is listed as "nontuberculous," the rôle of tuberculosis as an etiological factor in many of them cannot be ignored, even if not susceptible of proof.

Thirty-two cases of extensive pulmonary fibrosis, a few associated with emphysema, occupy the next place on the list of nontuberculous pulmonary disease. These undoubtedly represented the end result of previous disease processes, but in most cases no etiology could be assigned except for an occasional history of a previous "pneumonia." Tuberculosis and pneumonoconiosis were excluded, as far as possible, by the radiographic characteristics and the clinical history. Most of these cases had associated pleural changes. Despite the obscurity of the initiating factor, there could be little doubt that the resulting fibrosis had rendered these men unsuitable for military service.

Adenopathy of the hilar or mediastinal nodes comprised a group of 16 cases of unknown etiology. In 2 of these, tuberculosis was considered as the possible cause and in 3 others the radiographic appearance suggested sarcoidosis or tuberculosis. However, too much diagnostic weight was not given to these impressions.

Next in order of frequency was pneumonoconiosis, 11 cases of which were encountered, each confirmed by a history of occupational exposure. Hard-coal mining, foundry work and grinding with carborundum as an abrasive were the hazardous occupations in 10 cases. One man gave a history of exposure to asbestos in the form of heat-insulating fabrics. In 4 of these cases of pneumonoconiosis the radiographic findings indicated an associated tuberculosis.

Eventration of the diaphragm was cause for rejection in 8 cases. The left leaf of the diaphragm was involved in 4 instances, the right leaf in 3, while one case, with a history of injury of the chest, showed eventration of both leaves.

Mediastinal neoplasm with but 4 cases was a minor cause of disqualification. Other conditions which occurred rarely were calcified tuberculous cervical adenitis, substernal goitre with tracheal compression, and neoplasm of the ribs or scapula. Each of the following occurred singly: calcified pulmonary mass of unknown origin; cystic disease of the lungs, probably congenital; chronic bronchitis; luetic aortic aneurysm; and coarctation of the aorta.

DISCUSSION

The data presented in this report are based essentially on the interpretation of stereoscopic photoroentgenograms with the assistance of the conventional 14″ x 17″ film wherever indicated. Brief case histories and physical findings were also available to the roentgenologist and were utilized to the fullest extent. It is admitted that the diagnosis of activity in pulmonary tuberculosis from the X-ray findings alone is fraught with possibilities of error.

In the absence of a complete follow-up study of the cases rejected at the Buffalo Induction Station, it is instructive to compare the rates of rejection for pulmonary disease observed in this area with those recorded by Ehrlich, Schiller and Edwards (2) in a study based on the examination of 114,130 men from the Southern New York Recruiting District. These authors had the advantage of a complete diagnostic study in almost every case rejected. The population from which their cases were derived (New York City and vicinity) was similar to that on which the present study was based. The men examined in their survey, however, were chiefly Selective Service Registrants with a maximum age of 35 (later reduced to 28) and a minimum age of 21. The men from the Southern New York area therefore represented, in general, a younger age group than those examined in Buffalo. It should be added that the screening methods used in Southern New York were 14″ x 17″ paper roentgenograms in 70 per cent and single 4″ x 5″ photoroentgenograms in 30 per cent of the radiographic examinations.

Comparing the results of the two studies (table 7), it will be noted that the rate of rejection for pulmonary disease was 2.12 per cent in the Northwestern New York Recruiting District as against 1.14 per cent in the Southern New York area. The higher rate in the Buffalo area was the result of a greater percentage of arrested tuberculosis and of nontuberculous pulmonary disease. As regards the prevalence of active tuberculosis there is fairly close agreement between the two series—0.45 per cent and 0.38 per cent, respectively. The slightly higher percentage of arrested tuberculosis noted in the Northwestern New York District can be attributed to the generally older age level of the men examined. The experience reported in this study, as well as that of the authors cited in the Southern New York District, has demonstrated the greater prevalence of arrested tuberculosis with advancing age. The difference in the rejection rates for pulmonary tuberculosis in the two areas was therefore to be anticipated.

The disparity in the rejection rates for nontuberculous disease, however, cannot be so readily reconciled. The disproportion is most striking in those diseases which are the result of pneumonic or suppurative processes, namely, bronchiectasis, pneumonitis, diseases of the pleura and pulmonary fibrosis. Since these diseases are closely related in their pathogenesis and etiology, one must assume that there is a higher incidence of respiratory infections with their sequelae in the Northwestern New York area. Perhaps this is the result of the more severe climatic conditions that prevail in this part of the state. Whatever the reason, the rate of rejection for nontuberculous pulmonary disease was definitely higher in the Buffalo area.

There is a tendency to regard the discovery and the elimination of pulmonary tuberculosis from the Armed Forces as the sole benefit to be derived from the practice of routine chest roentgenography, while the screening out of other pulmonary diseases is relegated to a position of minor importance. Such an attitude, however, is scarcely justified by the experience gained from this analysis. The nontuberculous pulmonary diseases, as a group, accounted for the rejection of 0.55 per cent of the men examined, as compared with 0.45 per cent for active pulmonary tuberculosis. The significance of the nontuberculous diseases as a cause of disqualification for military service, therefore, is not to be minimized, and their diagnosis by means of routine roentgenography must be reckoned as a very valuable contribution of the Army X-ray program.

TABLE 7

Comparison of rates of rejection for pulmonary disease in the southern and northwestern New York Recruiting Districts

	EXAMINED	AGE	TOTAL REJECTED	TUBERCULOSIS			OTHER PULMONARY DISEASES
				Total	Active	Arrested	
Southern New York Recruiting district	114,130	21–35*	1.14%	1.01%	0.38%	0.63%	0.13%
Northwestern New York recruiting district	40,283	18–45*	2.12%	1.45%†	0.45%	1.00%	0.55%

* There were a negligible number of men above this maximum age in both groups.
† Reinfection type tuberculosis only.

CONCLUSIONS

1. The results of the routine chest radiographic examination of 40,283 men with 4″ x 5″ stereoscopic photoroentgenograms at the Buffalo Induction Station are presented.

2. Eight hundred fifty-six, or 2.12 per cent, were rejected because of pulmonary disease as revealed in the photoroentgenogram, of which 632, or 1.57 per cent, were for tuberculosis, and 224, or 0.55 per cent, for nontuberculous pulmonary diseases.

3. The cases of tuberculosis were divided as follows: there were 183 men, or 0.45 per cent, with active, or clinically significant tuberculosis; 403, or 1.00 per cent, with arrested tuberculosis; 40, or 0.10 per cent, with primary tuberculosis, unstable or healed; and 6, or 0.01 per cent, with lesions suspicious of tuberculosis.

4. Approximately 40 per cent of the men rejected were deferred temporarily. Thus, of the 632 cases rejected for tuberculosis, 258, or 0.64 per cent, were temporarily deferred in order to determine the stability of the lesion.

5. The rejection rate for tuberculosis varied considerably among the four categories of men examined, the oldest group showing the highest rate and the youngest group the lowest. The high rate among the older men was the result of a greater prevalence of arrested tuberculosis.

6. The various pulmonary diseases encountered, other than pulmonary tuberculosis, are reviewed.

7. Comparison of the rates of rejection obtained at the Buffalo Induction Station with those observed in the Southern New York Recruiting District, where all rejected registrants were followed up with a complete diagnostic study, showed essentially the same rejection rate for active tuberculosis in both localities. There was a somewhat greater prevalence of arrested tuberculosis and a considerably greater frequency of the nontuberculous pulmonary diseases in the Buffalo area. The greater prevalence of arrested tuberculosis in the Buffalo region was attributed to the generally older age level of the men examined.

CONCLUSIONES

1. Preséntase el resultado del examen radiográfico sistemático del tórax en 40,283 individuos, con estereofotorroentgenografías de 10 cm. x 12.5 cm. en la Estación de Reclutamiento de Buffalo.

2. A 856, o sea 2.12%, se les rechazó debido a afección pulmonar revelada por la fotorroentgenografía; en 632, o sea 1.57%, por tuberculosis; y en 224, o sea 0.55%, por neumopatía no tuberculosa.

3. Los casos de tuberculosis se dividieron en esta forma: en 183 hombres, o sea 0.45%, había tuberculosis activa o clínicamente significativa; en 403, o sea 1.00%, estacionada; en 40, o sea 0.10%, tuberculosis primaria, inestable o cicatrizada; y en 6, o sea 0.01%, lesiones sospechosas de tuberculosis.

4. Aproximadamente en 40% de los individuos rechazados se aplazó temporalmente el ingreso en el ejército; es decir que de los 632 casos rechazados por tuberculosis, 258, o sea 0.64%, fueron aplazados temporalmente a fin de determinar la estabilidad de la lesión.

5. El índice de rechazos por tuberculosis varió considerablemente en las cuatro categoría, de individuos examinados revelando el grupo de mayor edad el coeficiente mayor y el más joven el menor. El alto coefficiente en el primer grupo se debió a abundar más en el mismo la tuberculosis estacionada.

6. Repásarse las varias neumopatías descubiertas, aparte de tuberculosis pulmonar.

7. La comparación de los índices de rechazo de la Estación de Reclutamiento de Buffalo con los del Distrito de Reclutamiento del Sur de Nueva York, en el que se sigue observando a todos los inscritos rechazados y se hace un completo estudio diagnóstico, reveló mas o menos el mismo índice de rechazo por tuberculosis activa en ambas localidades. Hubo una incidencia algo mayor de tuberculosis estacionada y mucho mayor de neumopatías no tuberculosas en la zona de Buffalo, atribuyéndose esa frecuencia mayor de la tuberculosis estacionada a ser en general mayor la edad de los sujetos examinados.

REFERENCES

(1) DE LORIMIER, A. A.: X-ray examinations of the chest for the United States Army, M. Clin. North America, November, 1941, *25*, 1773.

(2) EHRLICH, D. E., SCHILLER, I. A., AND EDWARDS, H. R.: Army X-ray examination for tuberculosis, Am. Rev. Tuberc., 1943, *47*, 113.

(3) EDWARDS, H. R., AND EHRLICH, D. E.: Examinations for tuberculosis—roentgenographic findings of 41,809 inductees and 9,541 National Guardsmen in New York City, J. A. M. A., July 5, 1941, *117*, 40.

MILIARY TUBERCULOSIS OF THE BONE MARROW[1]

EMIL MARO SCHLEICHER[2]

Miliary tuberculosis affects the human bone marrow organ frequently enough, as judged by our autopsy records, that we may assume that biopsy of this organ should offer a means for detecting a tuberculous process.

Many methods have been devised to diagnose miliary tuberculosis early but according to a recent editorial by Myers (1) "fifty per cent or more of the diagnoses in the past have been possible only at post mortem."

A survey of the available literature revealed that Stahel (5) aspirated sternal marrow one day *ante mortem* from a terminal and known case of generalized miliary tuberculosis and observed a tubercle in the section made from the marrow clot. Because the tubercle was seen in the marrow of a terminal case the possibility of using the sternal aspiration method as a tool for detecting a miliary process was not seriously considered by clinical hematologists. I (4) have recently reported a case of pernicious anemia and miliary tuberculosis of the bone marrow organ showing the value of the sternal aspiration method and sectioning of gross sternal marrow units for detecting a tuberculous process early.

It is the purpose of this preliminary paper to present a series of patients in whom tuberculosis *per se* or as a complication was not suspected and thus (*a*) to stimulate interest in the simple and safe sternal aspiration method among students of tuberculosis and (*b*) to show that miliary tuberculosis can be demonstrated by obtaining from 1 to 2 cc. sternal marrow and serially sectioning a reasonable number of sternal marrow units.

The methods for obtaining sternal marrow and for making histological preparations from marrow units are published elsewhere (2, 6). For the sake of continuity, however, the procedures are outlined here. In the adult the preferred place of puncture is the middle portion of the body of the sternum at the second costal interspace. In a child less than two years of age the tibia may be used. It is imperative that a standard sternum needle is employed. Figure A shows the type of needle[3] used at the Minneapolis General Hospital.

The skin and periosteum are well infiltrated with a local anesthetic. The injected area is then massaged with a gauze sponge until there is little or no elevation of the skin. The distance between the skin and the surface of the anterior plate of the sternum is determined with the aid of a 22 gauge intravenous needle and the depth marked off by placing the tip of the thumb and index finger on the needle. The guard of the sternum needle is now adjusted until the needle part has the same length as the marked off part on the measuring needle. The sternum needle is now lengthened another 2 mm. by making three full turns of the guard. The latter maneuver takes care of the thickness of the normal anterior plate of the sternum ranging from 1 to 1.5 mm. and assures, at the same

[1] From the Department of Internal Medicine, Minneapolis General Hospital, Minneapolis, Minnesota.

[2] Parke Davis Fellow in Clinical Hematology.

[3] Made by V. Mueller & Co., Ogden Ave. and Van Buren St., Chicago, Illinois.

time, proper depth of the needle in the medullary cavity. The latter, in the adult, ranges in height from 5 to 9 mm. and in width from 2 to 3 cm.

A sudden "give sensation" is felt when the needle enters the medullary cavity. The instrument *in situ* should have the straight part of the guard plate parallel with the sterno-manubrial ridge (angle of Louis), thus assuring a firm embedding of the guard plate upon

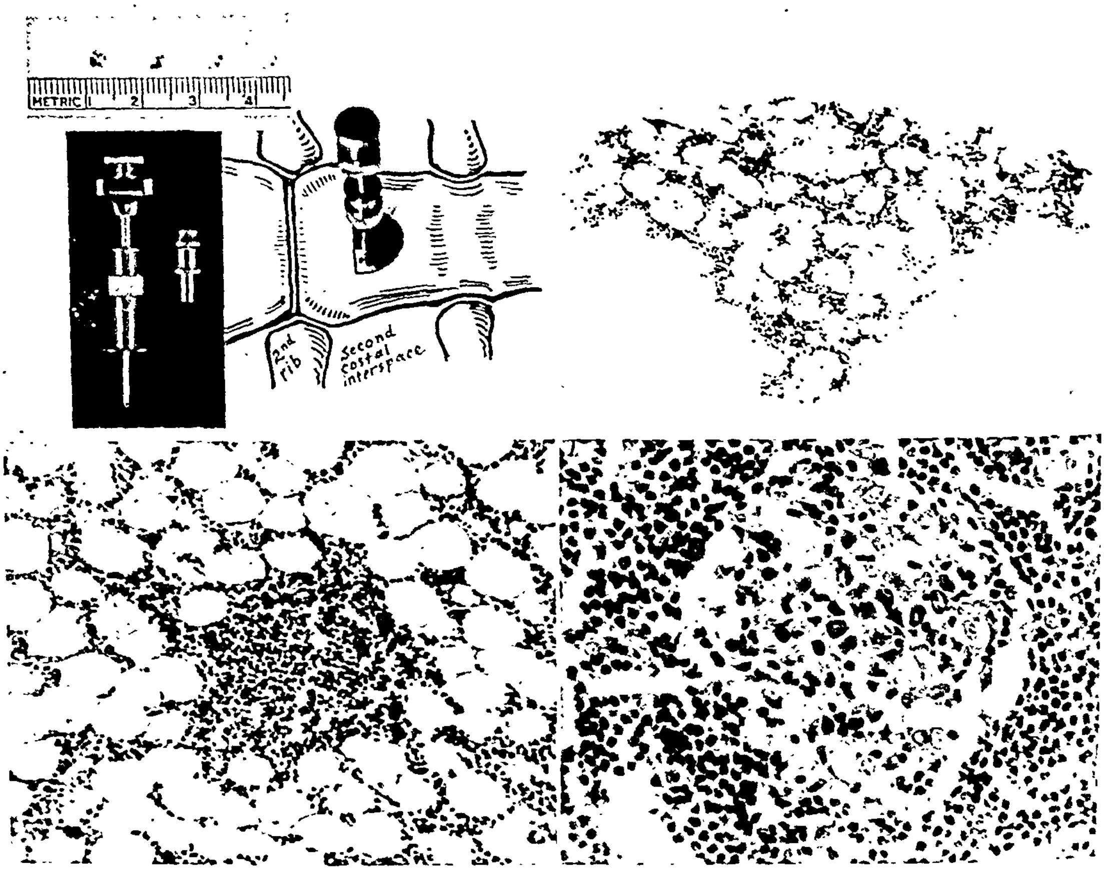


FIG. A. (Upper left) Sternum needle and correct position of the needle. Inset, variation of size of fixed sternal marrow units.

FIG. B. (Upper right) Section (about five micra in thickness) of a normal sternal marrow unit. H. & E stain.

FIG. C. (Lower left) Section of a sternal marrow unit showing fatty metamorphosis and a Hedinger-Askanazy lymph follicle. H & E stain.

FIG. D. (Lower right) Section of a sternal marrow unit showing a Hedinger-Askanazy lymph follicle with a germinal centre. Compare morphology with that of figure 3. H & E stain.

the skin and the needle in the bone and medullary cavity. (See figure A.) The stylet is then removed and, if its tip is blood-stained or a fat droplet is attached to it, an air-tight 20 cc. glass syringe reinforced with a metal adapter is attached to the needle head. The plunger is slowly withdrawn and as soon as marrow substance enters the syringe the plunger is rapidly withdrawn to the 10 cc. mark and held there until 1 or 2

cc. of marrow has been obtained. The specimen is placed immeditely in a paraffin-lined glass vial containing heparin[4] and mixed well by gently inverting the vial several times. The aspirated material is then examined for "marrow units" (marrow particles) by holding the vial against a light source and by slowly rotating the vial the units are encouraged to stick to the paraffin. Thus they are easily seen; their gross appearance may not only be studied but one is assured that marrow tissue has been obtained. Normal size of units is 0.5 to 1.0 millimeter.

The bone marrow specimen is now transferred to a paraffin-coated large watch-glass. The units either settle quickly or float. Whatever the case may be, the fluid part is either drained off by slowly tilting the receptable or the units are picked up with a medicine dropper. The units should be exposed to a fixing fluid as quickly as possible to prevent drying-up of the tissue. Fixing fluid may be poured directly over the marrow specimen if the units are few in number or are so small that they are difficult to see. I found that 10 cc. of neutral formaldehyde, 40 per cent, in 90 cc. physiological sodium chloride solution is a suitable fixing fluid for marrow tissue. The units are exposed to the fluid for at least ten minutes. The fixing fluid is then replaced with fresh fluid. Floating units should be picked up with a medicine dropper and transferred by it into the fresh fixing fluid. The latter should be renewed until the solution remains clear when the units are placed into the fluid for final fixation. Complete fixation occurs within one hour. The units are then transferred into graded alcohols, 50, 75, 85, 95 per cent, for one-half hour each, and then into absolute alcohol, dioxan or acetone, for fifteen minutes. If acetone is used for the final dehydration agent, overexposure should be avoided because brittleness of the marrow units will result. The specimens are kept in paraffin for one to two hours. The units must be well submerged to prevent drying of the tissue. The units are blocked, sectioned about five micra in thickness and stained with hematoxylin and eosin.

Table 1 is self-explanatory. Columns 10 to 13 show (*a*) the total number of sternal marrow units which were selected at random from individual yields, (*b*) the number of units showing tubercles and (*c*) the type of tubercle. The data show that if a reasonable number of sternal marrow units are examined a tuberculous process can be detected. From the data, one may presume that miliary tuberculosis is well disseminated in the bone marrow organ.

Figure A shows the sternum needle in correct position. The inset illustrates variations in size of fixed sternal marrow units. For the benefit of those who are not familiar with the histology of a marrow unit, a serial section (about five micra in thickness) of a normal sternal marrow unit is shown in figure B. It is imperative to stress that Hedinger-Askanazy lymph follicles, an example of which is shown in figure C, are not constituents of the normal human bone marrow organ at certain decades (2). The presence of such a structure means that pathological processes have created the follicle, but I could not detect the beginning of a tuberculous lesion within such a lymph follicle. Occasionally a follicle has a germinal centre (figure D). The inexperienced observer may mistake this type of follicle for an epithelioid tubercle. It is believed that the morphological difference between a lymph follicle with a germinal centre and an

[4] Dog liver heparin lot 152 is recommended or any heparin made according to the formula used in preparing lot 152. Made by Hynson, Wescott and Dunning, Inc., Baltimore, Maryland.

TABLE 1

KEY	CASE NUMBER	SEX	STERNAL MARROW	CHEST X-RAY FILM	GASTRIC WASHING	SPUTUM	GUINEA PIG INOCULATION	MANTOUX TEST 1:100	TOTAL NUMBER OF UNITS SECTIONED	NUMBER OF UNITS WITH TUBERCLES	EPITHELIOID TUBERCLES	CASEATED TUBERCLES	TUBERCLE BACILLUS DEMONSTRATED IN TUBERCLE	DIAGNOSIS BEFORE BONE MARROW EXAMINATION	CLINICAL STATUS OF PATIENT AFTER DIAGNOSIS OF TUBERCULOSIS	AUTOPSY FINDINGS
J. FI. MGH	1	M	Positive	Not done	Not done	Not done	Not inoculated	Positive	65	28	11	17	Yes	Known case of miliary tuberculosis	Expired same day	No autopsy
J. F. MGH	2	M	Positive	Not done	Not done	Positive	Bone marrow inoculation positive	Negative	20	12	1	11	Yes	Known case of pulmonary tuberculosis	Expired same day	No autopsy
P. C.	3	M	Positive	Positive	Not done	Negative	Bone marrow inoculation, still living when patient expired	Positive	5	1	0	1	Not checked	Known case of miliary tuberculosis	Expired six weeks later	Generalized miliary tuberculosis
H. K. G. San.	4†	M	Positive	Miliary-like shadows	Not done	Negative	Bone marrow inoculation, expired six days later	Positive	10	3	2	1	Yes	Boeck's sarcoid? Miliary tuberculosis?	Still living after three months	
C. B. MGH	5*	F	Positive	Not done	Not done	Not done	Not inoculated	Negative	15	9	1	8	Not checked	Carcinoma of rectum	Expired same day	Carcinoma of sigmoid colon. Generalized miliary tuberculosis
M. Y. MGH	6*	F	Positive	Pneumonic process of left lower lobe	Positive Done after Bone marrow diagnosis	Negative	Gastric Washing inoculation negative	Positive	100	8	7	1	Yes	Pernicious anemia refractory to therapy	Still living after five and one-half months‡	
R. P. MGH	7*	M	Positive	Negative	Not done	Not examined for tubercle bacilli	Not inoculated	Negative	12	10	5	5	Not checked	Typhoid fever	Expired same day	Generalized miliary tuberculosis
P. C.	8*	M	Positive	Negative	Negative	Did not raise sputum	Bone marrow inoculation positive	Positive	80	24	9	15	Yes	Bacterial endocarditis	Expired seven months later	No bacterial endocarditis. Miliary tuberculosis

* Miliary tuberculosis was not suspected.

† Bone marrow examined to aid differential diagnosis.

‡ After ten months patient developed tuberculous lymphadenopathy. Roentgenogram shows shadows of a miliary type in both lungs. Cultures from lymph node tissue and guinea pig inoculation are positive for *Mycobacterium tuberculosis*. Patient is still under observation.

epithelioid tubercle (figure 3) need not be pointed out. The photomicrographs show them clearly.

In general, the morphology of the developing tubercle follows the familiar pattern of this type of lesion. Figure 1 shows a relatively early miliary lesion near a small capillary (arterial) which takes a horizontal course through the

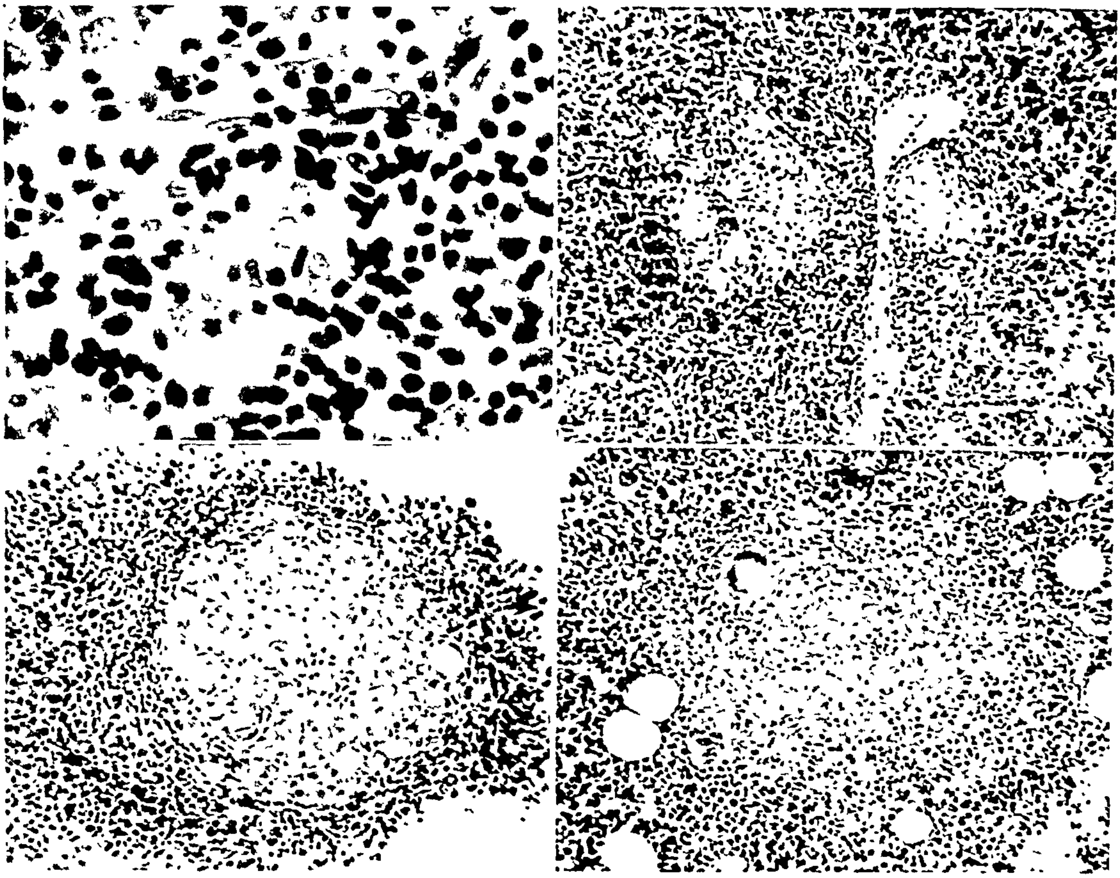


FIG. 1. (Upper left) Section of a sternal marrow unit showing early tubercle near a blood capillary (arterial). H & E stain.

FIG. 2. (Upper right) Section of a sternal marrow unit showing a large venous sinus with an epithelioid tubercle on each side. H & E stain.

FIG. 3. (Lower left) Section of a sternal marrow unit showing a characteristic epithelioid tubercle. H & E stain.

FIG. 4. (Lower right) Section of a sternal marrow unit showing a characteristic caseated tubercle. H & E stain.

section near the top of the photomicrograph. Below the blood vessel are some hypertrophic reticulum cells, several of which have already the appearance of the so-called epithelioid cell. Migrated small lymphocytes form a loose wall about the infected area. Demonstration of the tubercle bacillus within such an early lesion with the Cooper modification of the Ziehl-Neelsen stain was only

occasionally achieved. Figure 2 shows a venous sinus with a tubercle on each side. A conspicuous wall of lymphocytes surrounds the light staining epithelioid cells. Serial sections revealed that they were individual tubercles and not part of a large epithelioid tubercle. Figure 3 shows a representative of what is referred to in this paper as epithelioid tubercle. The structure is composed of closely packed epithelioid cells. There may or may not be one or more giant cells. Some small lymphocytes and occasionally a few polymorphonuclear neutrophils are dispersed within the epithelioid part of the tubercle. A distinct wall of small lymphocytes surrounds the periphery. At or near the marginal zone of this lymphoid wall small clusters of plasma cells and occasionally eosinophils have been noted. Although accumulation of eosinophils appears to be the exception rather than the rule. A caseated tubercle is shown in figure 4. The morphology of this type of tubercle is too well known to warrant a detailed description of the histopathology. In the majority of caseated tubercles the tubercle bacillus could be demonstrated.

DISCUSSION

A survey of the available literature failed to reveal that miliary tuberculosis of the human bone marrow organ has been demonstrated during life ahead of tell-tale physical signs, X-ray findings and other procedures designed to uncover this disease. Data derived from postmortem material and from terminal and known cases of pulmonary and generalized miliary tuberculosis showed that tuberculosis affects the bone marrow frequently enough to justify the use of the sternal aspiration method as a means for detecting the disease early. The use of a standard sternum needle makes the method a simple and safe procedure. I have not observed any serious injuries to the bone in our hospital. Serial aspirations can be done at short time intervals without great discomfort to the patient. Thus the possibility is open to obtain information with respect to the course of the disease and by the same token the effectiveness of chemotherapeutic agents may be studied in man. Aspirated sternal marrow can be directly inoculated into a guinea pig, cultured, imprinted or smeared on a glass slide (3) for the demonstration of the tubercle bacillus. Table 1 is self-explanatory.

SUMMARY

1. Miliary tuberculosis can be detected early by means of sternal aspiration and sectioning of gross sternal marrow units.

2. The possibility is suggested that the procedure may be a useful tool in diagnosis and prognosis in the field of tuberculosis.

SUMARIO

1. La granulia puede descubrirse tempranamente por medio de la aspiración del esternón y de cortes macroscópicos de médula ósea del mismo.

2. Es posible que este procedimiento resulte útil en el diagnóstico y pronóstico en el campo de la tuberculosis.

I wish to thank Dr. G. E. Fahr, Head of the Department of Internal Medicine, Minneapolis General Hospital, for his permission to publish the cases presented here; the residents and internes for their coöperation; Drs. J. A. Myers and E. T. Bell for the critical evaluation of my material. The photomicrographs were made by Mr. H. W. Morris, Campus Photographer, University of Minnesota.

REFERENCES

(1) Myers, J. A.: Dramatic advances on the tuberculosis front, Journal-Lancet, 1945, *65*, 160.
(2) Schleicher, E. M.: The volumetric pattern of aspirated normal human sternal marrow of males 18 to 40 years, Am. J. Clin. Path., 1944, *14*, 370.
(3) Schleicher, E. M.: Method for making imprints and direct smears from gross marrow units, Am. J. Clin. Path., Techn. Section, 1945, *9*, 8.
(4) Schleicher, E. M.: Pernicious anemia and miliary tuberculosis of the bone marrow organ, Am. J. Clin. Path., 1945, *15*, 402.
(5) Stahel, R.: Reaktionen um Granulationsgewebe im Knochenmark bei Miliartuberkulose und Boeckscher Krankheit, Folia Haemat., 1939, *61*, 345.
(6) Tucker, B.: A method for histologic preparations from gross marrow units, Minnesota Med. Technologist, 1945, *8*, No. 3.

PYOPNEUMOTHORAX [1]

Treatment of Two Cases with Penicillin

KENNETH T. BIRD, BORIS P. BUSHUEFF AND FRANCIS P. DAWSON

Pyogenic pleural infection may complicate the course of artificial pneumothorax. When it occurs, it presents a definite therapeutic challenge in the severely ill patient. Although penicillin has no effect *in vivo* or *in vitro* on the tubercle bacillus, it does exert a bacteriostatic action on many pyogenic infections (1, 2).

The value of penicillin in empyema complicating pneumonia (3), septicemia (4), thoracic surgical procedures and traumatic pneumothorax (5) has been well established.

Fortunately, pyogenic empyema complicating artificial pneumothorax is becoming less frequent (6). More clearly defined indications for induction of pneumothorax, early abandonment of technically unsatisfactory pneumothorax, judicious use of internal pneumonolysis, the use of primary thoracoplasty and the increasing availability of competent thoracic surgeons have all contributed to the diminishing incidence of this dreaded complication.

Penicillin, properly used, in pyogenic empyema may constitute the sole therapy required or, in the case of mixed infection tuberculous empyema, may be a most important adjuvant in total treatment.

CASE REPORTS

Case 1: A 35 year old single white female secretary was admitted to the Sanatorium on November 8, 1944. The patient was admitted to another sanatorium in August, 1939 with a diagnosis of moderately advanced pulmonary tuberculosis. Left pneumothorax was induced shortly after admission because of apical cavitation. She remained there until June, 1940. She had continued to receive biweekly pneumothorax refills. Six weeks before admission here, ten days after a pneumothorax refill, she suddenly developed diffuse left-sided chest pain with associated shortness of breath. She became anorectic and febrile. Five weeks, and again four and three weeks, before admission, air (amounts not known) was aspirated from her left chest with some relief of dyspnea. No fluid was noted on physical examination until two weeks before admission when an estimated pint of fluid was removed from the left pleural cavity. One week before admission, one quart of thick fluid was again aspirated.

On admission, November 9, 1944, X-ray examination of the chest was reported as follows: On the right, there is fibro-calcific infiltration from apex to third rib anteriorly. On the left, there is a hydropneumothorax with fluid to the level of the third rib anteriorly in the mammary line. There is marked displacement of the heart and mediastinum to the right.

On admission, temperature ranged from 100° to 102° F. and the patient was debilitated, weak and anorectic. Sputum remained consistently negative on seventy-two-hour concentration smear.

Aspiration was done November 9, 1944 with removal of 450 cc. of thick purulent fluid. Smear of this fluid showed many gram positive cocci in clusters which, after culture, were

[1] From Middlesex County Sanatorium, Waltham, Massachusetts.

identified as hemolytic *Staphylococcus aureus*. A second aspiration of 1,000 cc. of thick purulent fluid was done November 18, 1944. A pure culture of hemolytic staphylococcus was again obtained. No bronchopleural fistula was demonstrated with methylene blue injected intrapleurally.

The patient was started on 12,500 Oxford units of penicillin every three hours via intramuscular route. This was maintained for seven days. Daily intrapleural injections of 20,000 Oxford units of penicillin in 20 cc. of sterile physiological saline after aspiration and irrigation with saline were also done during this period. Fourty-eight hours after the

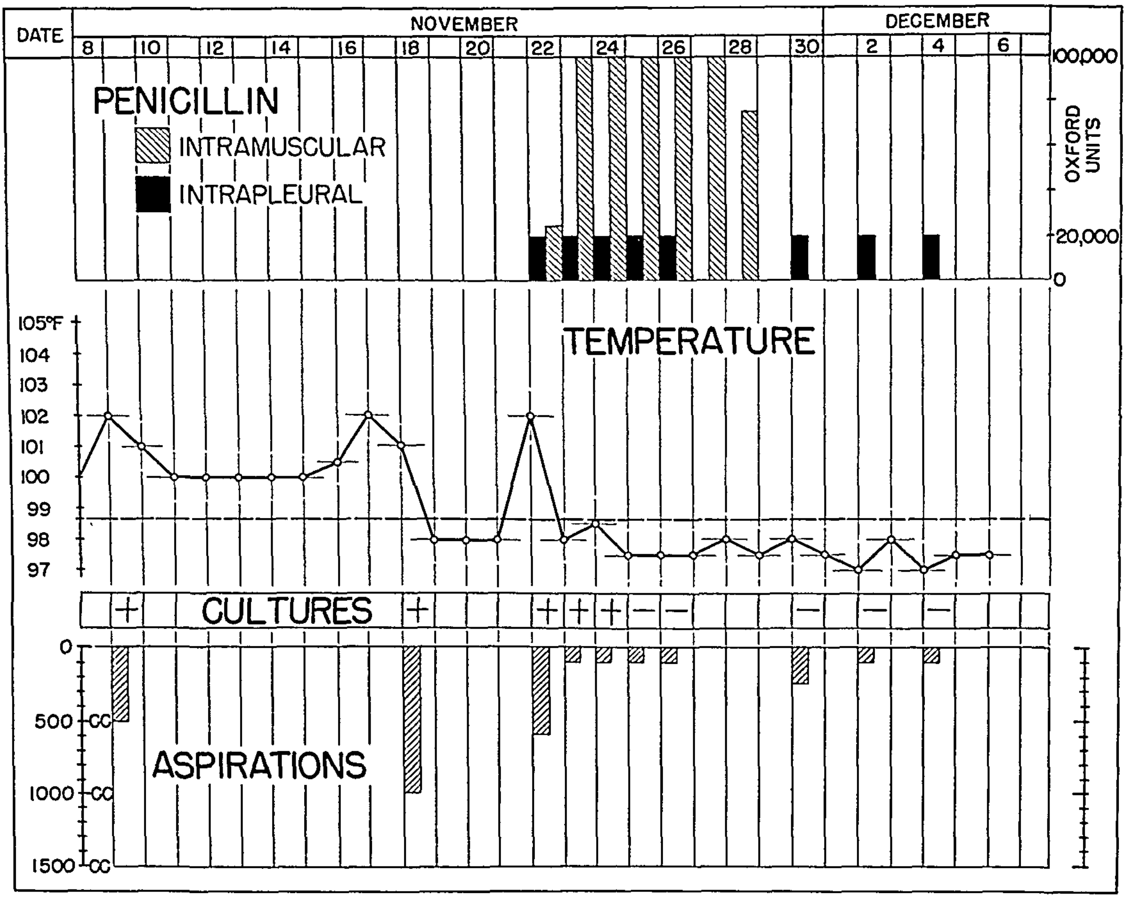


CHART 1

first injection of penicillin, there was a prompt abatement of toxemic symptoms with a coincidental fall in temperature. Patient has since remained afebrile. Fluid aspirated on the fourth day was sterile and remained so. Gradually, the aspirated fluid became thin and watery. Guinea pigs inoculated with concentrated pleural fluid aspirated on November 18 and November 26 were both negative for tuberculosis after six weeks. Further intrapleural penicillin was given as shown (chart 1). The left lung has since been allowed to completely reëxpand slowly. The patient has remained well.

Comment: This patient presumably developed a spontaneous pneumothorax after successful maintenance elsewhere of an artificial pneumothorax for a period

of five years and three months. *Staphylococcus aureus* empyema developed. No evidence of tuberculous empyema was obtained. This pyogenic empyema was successfully treated by penicillin. The collapsed lung was allowed to re-expand. Her course has since remained satisfactory.

Case 2: A 32 year old white married male insurance agent was admitted to the Sanatorium on October 13, 1944 with a diagnosis of moderately advanced pulmonary tuberculosis. The patient considered himself well except for a moderate cough productive of 2 to 4 drams of sputum daily for the past ten to eleven years. One year ago, he developed

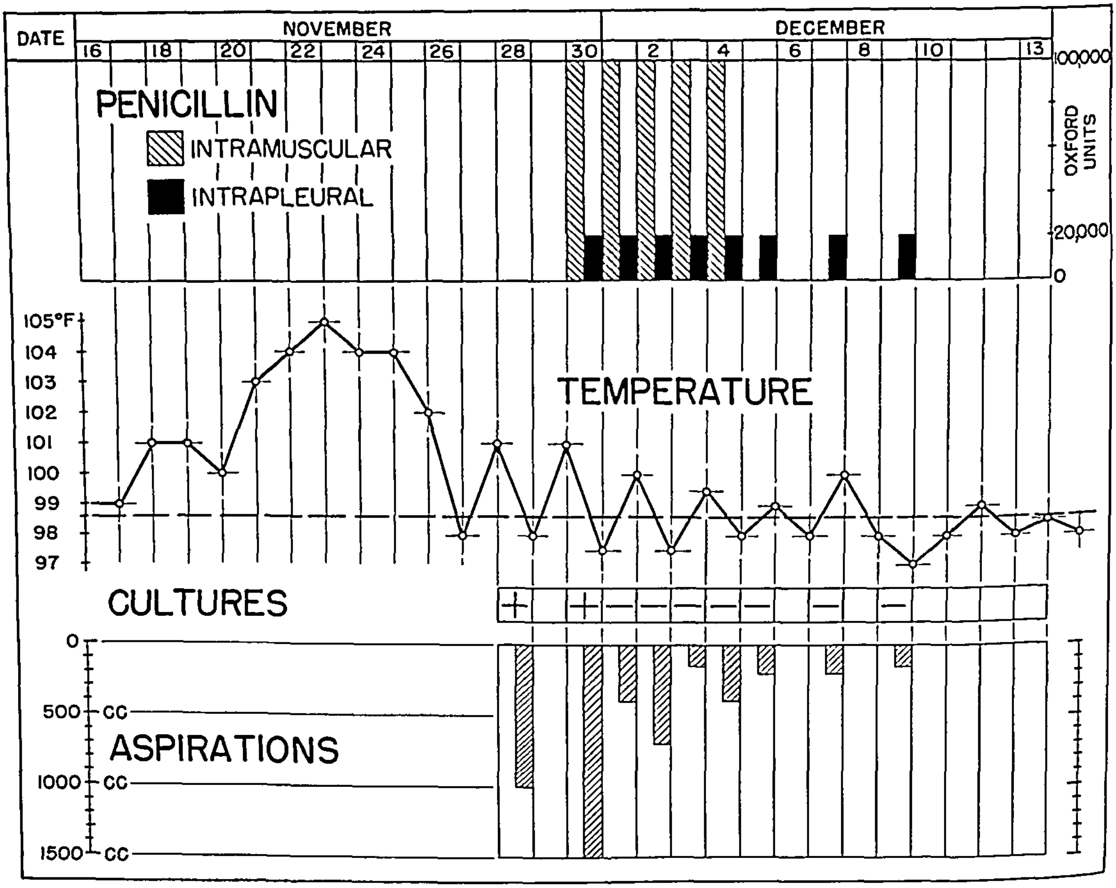


CHART 2

a fistula-in-ano. During the six months before admission he noted increasing fatigue and a weight loss of twenty pounds.

X-ray examination of the chest on admission, October 14, 1944 showed: On the right, there is mixed infiltration through the greater part of the upper lobe diminishing downward. There are numerous rarefied areas in the upper lobe suggestive of poorly defined excavation. On the left, there is mixed infiltration in the third interspace anteriorly.

On admission, temperature ranged from 99° to 100° F. Sputum was positive. Right pneumothorax was successfully induced on October 19, 1944. On November 17, 1944, when it appeared pneumothorax would probably be ineffective because of apical adhesions,

the patient became ill with a temperature of 101° F. Fluoroscopy revealed a small amount of fluid blunting the right costophrenic angle. The fluid rose above the level of the diaphragm coincident with a further elevation of his temperature to 103° F. He remained acutely ill. On November 25 and November 27 air was aspirated from his right pleural cavity with relief of dyspnea which had slowly developed. The fluid increased and on November 28, 1944, 1,000 cc. of thick purulent fluid was aspirated. Culture showed an abundant growth of alpha hemolytic streptococcus.

On November 30, 1944, 1,500 cc. of purulent fluid were aspirated and 20,000 Oxford units of penicillin in 20 cc. of sterile physiological saline were injected into the pleural cavity. At the same time, 12,500 Oxford units of penicillin intramuscularly was started. This was continued for five days. Aspiration of the chest followed by intrapleural injection of 20,000 Oxford units of penicillin was continued as shown (chart 2). By the second day of penicillin therapy the signs of toxemia rapidly disappeared. The patient regained his appetite and his temperature returned toward normal. Following the second intrapleural injection of penicillin the cultures remained negative. Autopsy of the guinea pig, inoculated November 28, 1944 with the originally aspirated pleural fluid, was positive for tuberculosis.

After discontinuation of penicillin, the patient was aspirated every two to five days followed by saline irrigations until December 14, 1944, when 1:6,600 azochloramid irrigations were used in an attempt to render the fluid less thick and viscous. Thereafter the procedure was repeated every two to three days until January 18, 1945, when the aspirated fluid changed to thin greenish-yellow. Successful three-stage thoracoplasty was completed May 3, 1945.

Comment: Early in the course of artificial pneumothorax, this patient developed a mixed infection tuberculous empyema undoubtedly due to rupture of a pleural adhesion. Alpha hemolytic streptococcus was isolated in pure culture. The response of the pyogenic infection to penicillin was prompt and complete. For the underlying parenchymal tuberculosis and the tuberculous empyema, thoracoplasty was performed.

DISCUSSION

The development of empyema during the course of artificial pneumothorax demands prompt and adequate bacteriological investigation. Aerobic and anaerobic culture for pyogenic organisms should be done as well as routine guinea pig inoculation and culture for tubercle bacilli.

Hemolytic streptococci, staphylococci and pneumococci, causative agents of the most common pyogenic empyemata, are fortunately penicillin sensitive (1, 2). Because of occasional strain variability and because other organisms may be isolated from pyogenic empyemata, routine determination of penicillin sensitivity of bacteria isolated, if penicillin therapy is contemplated, should, ideally, be performed. However, the bacterial species alone is generally regarded as an indication of susceptibility to penicillin (7). If the expected response does not occur, penicillin susceptibility determination is indicated. Such determination of penicillin sensitivity is easily done (8). Obviously, subjecting patients to vigorous therapy for infections caused by bacteria not responsive to penicillin is to be condemned.

Penicillin was used intramuscularly and intrapleurally in these 2 cases since it was felt that combined therapy would offer the best opportunity to control the debilitating infections. It was also thought that the high tissue concentration of penicillin, brought about by parenteral injection (9), might be of value in preventing local complications occasionally caused by repeated aspirations. Although there is no general agreement as to penicillin administration (1), recent evidence, obtained from a careful study of traumatic pyopneumothorax, indicates that, with infection localized to the pleural cavity, intrapleural penicillin alone is sufficient (5). On the other hand, parenteral penicillin alone will usually not suffice, for adequate therapeutic levels cannot be maintained in pleural fluid by this route (5, 10).

As yet the optimum dosage of penicillin in various infections has not been fully established. In fact, "the dosage of penicillin will vary from one patient to another depending on the type and severity of infection" (1). The recommended dosage of penicillin (as the sodium salt) in empyema varies but, in general, ranges from 20,000 units to 40,000 units (intrapleural alone) daily or every other day (1, 5). Some have suggested intrapleural penicillin twice daily in overwhelming pyogenic empyema (1). It should be realized that six to eight hours are required for a maximum antibacterial effect of penicillin (11). Thus, too frequent use intrapleurally or irrigation of the pleural cavity with penicillin is misuse. In practice, immediately after thoracocentesis, which should be supplemented by saline irrigation, penicillin, dissolved in physiological sterile saline solution, is injected directly into the pleural cavity. If systemic infection exists, parenteral penicillin in adequate dosage is also indicated, for example, 100,000 units daily in divided doses.

The response to penicillin in pyogenic empyema is usually marked, the toxemic symptoms disappearing or at least rapidly abating within twenty-four to forty-eight hours; that is, or course, if the causative organism is penicillin sensitive. But one must be aware of two potential pitfalls. The first is that, although there may be an early and dramatic clinical improvement following initiation of penicillin therapy, premature discontinuation or inadequate dosage may allow a later recrudescence of the infection or, more important perhaps, may allow the development of penicillin resistant organisms (12). The latter is most undesirable, for penicillin fastness of bacterial strains is apparently permanent (13). The second is the observed fact that thick pus usually persists several weeks after clinical improvement and conversion to a sterile fluid (5). However, thoracotomy may occasionally be necessary, especially in the presence of a staphylococcal empyema (7).

Obviously then, repeated culture of the aspirated fluid is important for continuation of therapy is guided by the presence or absence of viable organisms.

Duration of therapy depends upon the clinical response less than upon the results of continued bacteriological study of the empyema fluid. Ordinarily, several intrapleural injections are required. Penicillin must be given until the infection is eliminated. A minimum of three intrapleural injections is usually required to effect a cure (7) but more prolonged treatment is often necessary.

Penicillin, unlike the sulfonamides, is effective in the presence of pus, necrotic tissue or para-aminobenzoic acid (14). Nevertheless, there is general agreement that the supplemental procedure of repeated, often daily, aspiration of the empyema fluid is essential. Culture of this aspirated fluid will thus serve to indicate the duration of therapy.

Reactions caused by penicillin are uncommon (7). Those, such as thrombophlebitis or chills with or without fever occurring after intravenous injection and local muscle cramps, headache or faintness with flushing of the face or pain at the site of injection occurring after intramuscular use, are thought to be due to impurities in the penicillin. These will undoubtedly become even less frequent with the increased purity of penicillin now in use. It appears likely that the most common reaction following intrapleural injection of penicillin may well prove to be transient and unimportant urticaria. In fact, urticaria was the most common complication encountered in a large series of miscellaneous infections treated by penicillin given by various routes (12). Here again, this reaction was thought to be due primarily to toxic impurities. Urticaria may persist for three to five days and does not interfere with continuation of therapy. True penicillin sensitivity is rare but apparently does not prevent continued usage of the drug (15).

Finally, the use of penicillin in pyogenic empyema developing during artificial pneumothorax enables one to treat more successfully this undesirable complication. Penicillin exerts no effect on the tuberculous infection of either the parenchyma or the pleura. But penicillin may prevent an otherwise severe and debilitating infection from leading to a prolonged period of incapacitation or often to a fatal termination.

CONCLUSIONS

Two illustrative cases of severe pyogenic empyema, complicating artificial pneumothorax and successfully treated by penicillin, are presented.

The indications for and the dosage of penicillin in pyogenic empyema are discussed.

It is stressed that the use of penicillin does not supplant the treatment required for the control of the tuberculous infection.

CONCLUSIONES

Preséntanse 2 casos típicos de empiema piógeno grave que complicaba un neumotórax terapeútico y fueron tratados con éxito con la penicilina.

Discútense las indicaciones y la posología de la penicilina en el empiema piógeno.

También recuérdase que el empleo de la penicilina no suplanta al tratamiento necesario para cohibir la infección tuberculosa.

REFERENCES

(1) War Production Board: Penicillin Bulletin., December 1, 1944.

(2) Blake, F. G.: The therapeutic indications of the sulfonamides and penicillin, J. A. M. A., 1945, *127*, 517.

(3) HARFORD, C. G., MARTIN, S. P., HAGEMAN, P. O., AND WOOD, B. W., JR.: Treatment of staphylococcic, pneumococcic, gonococcic and other infections with penicillin, J. A. M. A., 1945, *127*, 253.

(4) DAWSON, M. H., AND HOBBY, G. L.: The clinical use of penicillin: Observations in 100 cases, J. A. M. A., 1944, *124*, 611.

(5) D'ABREU, A. L., LITCHFIELD, J. M., AND THOMPSON, S.: Penicillin in the treatment of war wounds of the chest, Brit. J. Surg., (Supplement to Vol. 32, July, 1944), 1944, *32*, 179.

(6) RAFFERTY, T. N.: Artificial Pneumothorax in Pulmonary Tuberculosis, New York, 1944.

(7) ANDERSON, D. G.: The treatment of infections with penicillin, New England J. Med., 1945, *232*, 400.

(8) RAMMELKAMP, C. H., AND MAXON, T.: Resistance of *Staphyloccus aureus* to action of penicillin, Proc. Soc. Exper. Biol. & Med., 1942, *51*, 386.

(9) RAMMELKAMP, C. H., AND KEEFER, C. S.: The absorption, excretion and distribution of penicillin, J. Clin. Investigation, 1943, *22*, 425.

(10) TILLETT, W. S., CAMBIER, M. J., AND MCCORMACK, J. E.: Treatment of lobar pneumonia and pneumococcal empyema with penicillin, Bull. New York Acad. Med., 1944, *20*, 142.

(11) KEEFER, C. S., BLAKE, F. G., MARSHALL, E. K., JR., LOCKWOOD, J. S., AND WOOD, B. W., JR.: Penicillin in the treatment of infections: A report of 500 cases, J. A. M. A., 1943, *122*, 1217.

(12) LYONS, C.: Penicillin therapy of surgical infections in the U. S. Army, J. A. M. A., 1943, *123*, 1007.

(13) SCHMIDT, L. H., AND SESLER, C. L.: Development of resistance to penicillin by pneumococci, Proc. Soc. Exper. Biol. & Med., 1943, *52*, 353.

(14) ABRAHAM, E. P., CHAIN, E., FLETCHER, C. M., FLOREY, H. W., GARDNER, A. D., HEATLEY, N. G., AND JENNINGS, M. A.: Further observations on penicillin, Lancet, 1941, *2*, 177.

(15) CRIEP, L. H.: Allergy to penicillin, J. A. M. A., 1944, *126*, 429.

TRANSCUTANEOUS TUBERCULIN TEST (CORPER)

Its Evaluation as Compared with the Mantoux Test

LAWRENCE W. HOLDEN[1]

Tuberculin testing has been recognized for some time as an essential part of the tuberculosis case-finding programs of high schools and colleges. The Mantoux test has been generally accepted of recent years as the most reliable, but it offers several rather serious drawbacks. The test must be administered by trained medical personnel. If the two-dose method is used, students frequently fail to return for the second dose or for the reading of the second dose. Large single doses require only one return visit, but the percentage of severe local and general reactions runs much higher than with the former method. Some physicians also fear the lighting up of quiescent tuberculous lesions if a strong reaction is produced. The Vollmer patch test, although obviating the mental anguish of injection, has the disadvantage of its slow reaction as well as adhesive tape reactions occurring in certain persons, and its efficiency may be questioned because of its mode of application.

Corper and Cohn (1) produced a highly potent autolytic tuberculin, which was proved to be identical in its biological activity with the purified protein derivative (PPD) of tuberculin. In order to obviate some of the disadvantages of the Mantoux, Vollmer and other tuberculin tests, this autolytic tuberculin was powdered and incorporated into a non-irritating and non-allergizing, transparent, liquid preparation which would dry on the skin in a few minutes after application. This has been called "The Transdermal or Transcutaneous Tuberculin Test" (2).

Because of the apparently satisfactory results of the transcutaneous tuberculin test (Corper) as applied to a group of tuberculous and nontuberculous soldiers (3), it was decided to try it more extensively on student groups. Consequently, the tests[2] were made on several groups of freshmen students entering the University of Colorado in the 1944–1945 school year.

The transcutaneous tuberculin testing material furnished was a suspension of powdered autolytic tuberculin in a liquid medium. The mixture was found to be stable for at least four months at room temperature. After being stirred up in the bottle, by means of a small glass rod, to get the tuberculin into suspension, a streak of the wet material 3 by 15 mm. was painted transversely on the unprepared or acetone cleaned skin of the flexor surface of the forearm. The test material required approximately two minutes to dry. The students were instructed to avoid washing the site of application or removing the test material. When the students returned in forty-eight hours for the reading of the tests, almost all of the dried material was found to be adherent to the skin, even after

[1] Director, Student Health Service, University of Colorado, Boulder, Colorado.

[2] The tuberculin was furnished by Dr. H. J. Corper, Research Department, National Jewish Hospital, Denver, Colorado.

bathing. A few of the tests had been removed by frequent water immersion of the arm of students who were dish-washers. Occasionally it was found necessary to remove the dried test material with acetone in order to observe the skin beneath it. The reactions which were called positive varied from one or more pinpoint, papular, erythematous areas without edema to an erythematous area 10 by 30 mm. with edema extending slightly beyond the area of redness. Complete absence of erythema was considered to be a negative reaction.

In the following report the transcutaneous tests were compared with controls done with intracutaneous PPD tests. The tuberculin for both tests was prepared from the same original bacillary cultures by Corper and Cohn. Commercial tuberculin was not used.

The tests were first tried on a group of students entering the University in July, 1944. A transcutaneous tuberculin test was applied to the unprepared skin of the right forearm, and an intracutaneous test using 0.0001 mg. PPD was injected simultaneously into the left forearm. Both tests were read after forty-eight

TABLE 1

Comparison of transcutaneous and intermediate dose Mantoux tests

TEST	NUMBER TESTED	NUMBER POSITIVE	PER CENT POSITIVE
A) July, 1944:			
PPD 0.0001 mg.	277	32	11.6
Transcutaneous	277	27	9.8
B) March, 1945:			
PPD 0.0002 mg.	241	33*	13.7
Transcutaneous	241	27†	11.2

* 14 of these were negative to transcutaneous; 10 out of this 14 showed calcifications in the lungs.

† 8 of these were negative to the PPD; 3 out of the 8 showed calcifications in the lungs.

hours. Another group of students entering in March, 1945 was tested in the same manner, but in this second group the skin was cleaned with acetone before application of the transcutaneous test, and 0.0002 mg. PPD was used for the intracutaneous test. The results of both groups are given in table 1.

Since the percentage of positive reactors was lower than anticipated in the July group, another group of new students, entering in September, 1944, was tested with the transcutaneous and the standard two-dose intracutaneous tests. The group was first tested simultaneously with the transcutaneous and the intracutaneous tests using 0.000,02 mg. PPD for the latter. At the end of forty-eight hours, all negative reactors were retested with 0.005 mg. PPD. It had been planned to retest these individuals simultaneously with the transcutaneous test, but, due to lack of testing material at the time, only 96 of the 258 negative to the first dose were retested with the transcutaneous test. The results are shown in table 2.

The apparent discrepancy between the first and second transcutaneous tests

in the group shown in table 2 prompted the testing of another new group in November, 1944, by means of two simultaneous transcutaneous tests. One transcutaneous test was applied to each forearm. An unusually large group of entering students caused a lack of experimental test material with the result that

TABLE 2

Comparison of transcutaneous and two-dose Mantoux tests

A) Results of simultaneous tests September, 1944:

Tests*	PPD_1+ TT_1+	PPD_1+ TT_1-	PPD_1- TT_1+	PPD_1- TT_1-	PPD_2+ TT_2+	PPD_2+ TT_2-	PPD_2- TT_2+	PPD_2- TT_2-
Number	22	12	26	233	15	27	5	49

B) Summary of above:

TEST	NUMBER TESTED	NUMBER POSITIVE	PER CENT POSITIVE
PPD_1 (0.000,02 mg.)	293	34	11.7
1st transcutaneous	293	48	16.4
PPd_2 (0.005 mg.)	96	42†	43.7
2nd transcutaneous	96	20‡	20.8
PPD_2 (0.005 mg.) (No transcutaneous)	162	52	32.1
Combined PPD_1 and PPD_2	293	123	43.3
Combined TT_1 and TT_2	293	62	21.2

* TT_1 and TT_2 = 1st and 2nd transcutaneous tests.

† Some doubtful positive tests.

‡ Fourteen of this number had been negative to TT_1. Four were positive to TT_1 and negative to TT_2.

TABLE 3

Transcutaneous tests alone (November, 1944)

A) Two simultaneous transcutaneous tests:

Both negative	211
One positive and one negative	35 (12.2%)
Both positive	40 (14.0%)
Number tested	286

B) Single transcutaneous test:

Number tested	*Number positive*	*Per cent positive*
502	100	19.9

the last 502 students received only a single transcutaneous test. The results of both groups are shown in table 3.

A summary of tests from all groups is given in table 4.

The transcutaneous test material was somewhat difficult to use since it was found necessary to keep it constantly stirred to prevent settling of the powdered

tuberculin to the bottom of the bottle. Clumping of particles of tuberculin was noted, particularly when the liquid material became thickened from evaporation of the volatile solvent when the bottle was opened frequently during use. The last portion of each bottle had to be discarded since it proved too thick for use. No attempt was made to thin the thickened material with solvent, and thus salvage the residue.

The higher percentage of reactors observed with the transcutaneous tests in the September and November, 1944 groups as compared with the July, 1944 and March, 1945 groups is unexplained. This degree of difference is frequently encountered in different groups in any type of tuberculin testing. One possible explanation for variation in the different groups tested with the transcutaneous material is the difference in the thoroughness of grinding the tuberculin in different batches of material since it had been prepared by hand with mortar and pestle.

TABLE 4

Summary of tables 1 to 3

TEST	NUMBER TESTED	NUMBER POSITIVE	PER CENT POSITIVE
Transcutaneous	1,599	291*	18.2
Mantoux:			
A) Single intermediate dose PPD 0.0001 mg. PPD 0.0002 mg.	518	65	12.5
B) Two-dose PPD 0.000,02 mg. and PPD 0.005 mg.	293	128	43.3

* This includes the 35 cases from table 3 which gave simultaneous positive and negative reactions.

Most of the transcutaneous tuberculin tests did not become positive until the second day, although those tests which were strongly positive showed obvious erythema in from twelve to twenty-four hours after application. In the September, 1944 group, out of 62 positive transcutaneous tests, 4 were not positive until ninety-six hours. How many other such delayed reactions went unnoticed is not known. Probably there were not many, as they would likely have been noticed and reported.

No generalized or systemic reactions were observed with the transcutaneous tuberculin test. The strongest reaction seen with this test was in an individual who had a previous 3-plus reaction to 0.1 mg. OT. In this case, the transcutaneous test produced an area of erythema and edema 10 by 30 mm. Corper (3) has stated that, in frankly active tuberculous soldiers, the transcutaneous tuberculin test produced strongly positive reactions with vesiculation of the skin, "but never

reached alarming proportions." Dr. Charles J. Kaufman, at the National Jewish Hospital, in 1944 found 169 (95 per cent) positive tests in 178 tuberculous patients. Recheck of the 8 negative reactors a week later gave 100 per cent positive results. A few of these patients showed lymphangitis, and one showed hemorrhage at the site of the transcutaneous test. Dr. Bret Ratner, in a personal communication to Doctor Corper, reported both transcutaneous and Mantoux tests positive in 21 out of 22 tuberculous children. No severe reactions were found.

The rather high percentage of reactors to the two-dose transcutaneous test using PPD seems higher than expected for students in the Rocky Mountain region, but it is possibly due to the fact that many of the students come from metropolitan areas out of the state as well as to the high purity of the tuberculin used. The figure, 43.3 per cent positive, does not differ greatly from that found in many other university health services. Canuteson (4) found 40.1 per cent positive with the usual two-dose test at the University of Kansas in 1938.

Chest X-ray films (14 by 17 inch) were taken of all reactors, regardless of which test was positive. It was noted that no calcifications were found in the lungs of any person positive only to the larger dose of PPD. In the March, 1945 group of 341 students, 14 out of 33 positive to the intermediate dose of PPD were negative to the transcutaneous test. Of these 14 students, 9 showed X-ray evidence of pulmonary calcifications. Of the 8 cases having negative intracutaneous and positive transcutaneous tests, 3 showed definite pulmonary calcifications. No cases of active tuberculosis were found in this entire series. The literature contains many statistics showing the presence of roentgenological evidence of calcified pulmonary lesions in a fair percentage of cases negative to 0.005 mg. PPD. Stiehm (5) found, in students negative to 0.005 mg. PPD, 6 per cent with calcified pulmonary lesions. Tice (6) found, in children negative to 0.0005 mg. PPD, 18 per cent with calcifications. Others have reported much higher percentages. Undoubtedly the finding of pulmonary calcifications, particularly in the hilar area, depends largely upon the roentgenologist viewing the films.

It was noted particularly that there were no strong positive (3-plus and 4-plus) reactions to PPD_2 in those cases which had been negative to PPD_1. Doubtful or suspicious positive tests with PPD_1 were invariably strongly positive with PPD_2. No 4-plus reactions were seen in this series.

DISCUSSION

The above findings bring up the often asked question of when the dose of a given tuberculin becomes large enough to produce nonspecific reactors. Furcolow, Hewell, Nelson and Palmer (7) feel that nonspecific reactions are liable to occur above 0.0001 mg. PPD and that this dose should discover all active cases of tuberculosis. They have shown also that almost all individuals will react if a large enough dose is given. They produce ample evidence to prove that the nonspecificity of the tuberculin reaction increases as the dosage of tuberculin is increased. Long (8) had previously shown that 94 per cent of his white tubercu-

lous patients reacted to 0.000,02 mg. PPD. On the contrary, Stiehm (5) reported in 1939 that, if he had used only the first dose of PPD in his five-year tuberculosis program among University of Wisconsin students, he would have failed to find 22.5 per cent of his 71 active cases of pulmonary tuberculosis. About one-third of this number had given suspicious positive reactions to the first dose of PPD, however. Possibly an intermediate dose would have produced more reactors. Narodick (9) reported that, "of the 332 cases of active pulmonary tuberculosis, 104 (32 per cent) had negative PPD_1. Of these 104 cases, 102 (98 per cent) responded to the PPD_2 test."

There are many variables to be considered in the interpretation of the tuberculin reaction which is based upon tuberculous allergy and not upon tuberculosis *per se* (10). The degree of sensitiveness to tuberculoprotein seems to fluctuate with the activity of tuberculous lesions, with the seasons, with the temperature and circulation of the skin at the site of the test, and probably with other unknown factors as well. Reversal of the tuberculin reaction is not uncommon, even in the presence of roentgenological evidence of pulmonary calcifications thought to be tuberculous in origin. This phenomenon as well as the entire tuberculin testing problem has been thoroughly discussed by Tice (6). The tuberculin reaction is difficult to interpret and, at best, should not be taken as a specific test which always shows the presence or absence of tuberculous infection. In spite of this fact, the tuberculin test is still classed as a very valuable single biological test useful in diagnosis and surveys.

It is this author's opinion that the ideal method of mass survey in college tuberculosis case-finding programs would be yearly tuberculin tests of all students, regardless of previous reactions. This would be combined with yearly chest X-ray films, regardless of tuberculin reaction. In this way X-ray films of negative reactors would give basis for comparison should the tuberculin reaction subsequently become positive or suspicious shadows arise in subsequent films. The use of 4 by 5 inch or possibly 70 mm. chest X-ray films combined with the tuberculin test would reduce the cost of such programs sufficiently to bring it within reach of most college health services. Many states now have mobile chest X-ray units, which are already being utilized for this purpose.

As a result of the experimental work here presented, it is felt that a more finely ground tuberculin than that used would produce more intimate contact with the skin and make the test more constant. Possibly sonic vibration would produce the desired fineness of the tuberculin which could be more easily kept in suspension. Putting up the liquid tuberculin in individual dose capillary tubes would save material and prevent drying out.[3]

The ease with which the transcutaneous tuberculin test may be given and frequently repeated as well as the absence of physical and emotional trauma makes this test most acceptable to the patient. The inconstant results with the transcutaneous material used here, however, make its value doubtful from the stand-

[3] It is understood that the Transcutaneous Tuberculin Test (Corper) is to be manufactured by Parke, Davis & Company.

point of the physician. It is felt that many more tests with an improved product are indicated before the test may be properly evaluated.

SUMMARY

The "Transcutaneous Tuberculin Test" (Corper) consisting of the application to the skin of a stable, quick-drying, liquid suspension of a highly potent autolytic tuberculin, was compared with the Mantoux intracutaneous tuberculin test done with PPD prepared from the same original bacillary cultures. The tests were done for the most part simultaneously on 1,599 freshmen university students.

The transcutaneous tuberculin test compared favorably with the Mantoux test done with an intermediate dose (0.0002 mg.) of PPD. The transcutaneous test produced a higher percentage of reactors than the usual first dose (0.000,02 mg.) of PPD but produced only about one-half as many reactors as the two-dose intracutaneous test using 0.000,02 mg. and 0.005 mg. of PPD. Two simultaneous transcutaneous tests done on the same individuals in a group of 286 students showed both tests positive in 40 cases and one positive and one negative test each in 35 cases. This failure to agree is thought to be due partly to the fact that the tuberculin was not ground finely enough to keep it in suspension. Suggestions for the improvement of the experimental material are given.

The "Transcutaneous Tuberculin Test" (Corper) at its present stage of development cannot be considered reliable enough to recommend it for general use. Further testing of large groups with an improved product is indicated.

SUMARIO

Compárase la "Transcutirreacción a la Tuberculina" (Corper), que consiste en la aplicación a la piel de una composición líquida y estable que se seca rápidamente de una potentísima tuberculina autolítica, con la intracutirreacción de Mantoux ejecutada con PPD obtenido de los mismos cultivos bacilares primitivos. Las pruebas se realizaron en su mayoría simultáneamente en 1,599 estudiantes recién ingresados en la Universidad.

La transcutirreacción se comparó favorablemente con la Mantoux ejecutada con una dosis intermedia (0.0002 mg.) de PPD, obteniendo un porcentaje mayor de reactores que la primera dosis habitual (0.000,02) de PPD, pero sólo obtuvo la mitad de reactores que la intracutirreacción en 2 dosis: una de 0.000,02 mg. y otra de 0.005 mg. de PPD. Dos transcutirreacciones simultáneas ejecutadas en los mismos individuos de un grupo de 286 estudiantes resultaron positivas: en 40 ambas veces y en 35 una vez positiva y una vez negativa. Según parece, este desacuerdo se debe en parte a que la tuberculina no fué triturada lo suficientemente para mantenerla suspendida. Ofrécense indicaciones destinadas a mejorar la sustancia de experimentación.

En su actual etapa de desarrollo no puede considerarse que la "Transcutirreacción a la Tuberculina" (Corper) sea suficientemente fidedigna para recomendarla para empleo general. Queda indicada la comprobación ulterior de grupos numerosos con un producto perfeccionado.

REFERENCES

(1) Corper, H. J., and Cohn, Maurice, L.: Autolysis of tubercle bacilli and the production of tuberculin (tuberculoprotein), Am. Rev. Tuberc., 1943, *48*, 443.
(2) Corper, H. J.: A proposed transdermal or transcutaneous tuberculin test, Bull. Am. Acad. Tuberc. Physicians, 1941, *5*, 111.
(3) Corper, H. J.: Comparative results with transdermal (or transcutaneous) and intracutaneous tuberculin tests, J. Lab. & Clin. Med., 1944, *29*, 398.
(4) Canuteson, R. I.: A comparison of the intermediate and the two-dose tuberculin tests, Journal-Lancet, 1939, *59*, 128.
(5) Stiehm, R. H.: A review of a five-year tuberculosis program among University of Wisconsin students, Am. J. M. Sc., 1939, *197*, 517.
(6) Tice, Frederick: Bull. City of Chicago Municipal Tuberculosis Sanitarium, 1938, 1939, 1940, Vols. 18, 19, & 20, pp. 1-92.
(7) Furcolow, Hewell, Nelson and Palmer: Pub. Health Rep., 1941, *56*, 1082.
(8) Long, Esmond, R.: The tuberculin test: Its value and its limitations, Am. Rev. Tuberc., 1939, *40*, 607.
(9) Narodick, Philip H.: The tuberculin patch test: Its evaluation as compared to the Mantoux PPD. test, Northwest Med., 1942, *41*, 193.
(10) Corper, H. J., and Cohn, Maurice L.: Intoxication in tuberculosis, Am. Rev. Tuberc., 1940, *41*, 71.

ANATOMICAL STUDIES ON HUMAN TUBERCULOSIS[1]

XXI. The Reinfection Complex

Additional Observations

KORNEL TERPLAN

In collaboration with Charles Becker

In several previous papers (1) anatomical findings were presented proving that an exogenous reinfection might result in the formation of a typical tuberculous complex (Ranke), similar in every respect to the parenchymal focal lesion known as the primary focus and to its associated (regional) lymph node changes. In the 10 cases discussed in one of these papers (VII) the complex of the true primary infection was clearly established in a firm stony and partly ossified state, while the reinfection complex was of comparatively recent structural age, mostly caseated or sometimes in cheesy-chalky condition. These were incidental findings of no clinical significance. In another group of cases (reported in paper XI) only the reinfection had led to the typical picture of a Ranke complex, while from the old primary infection no trace was left other than a typical healed old primary focus in firmly calcified or ossified state. The old primary lesion in these cases was found in another lobe than the one containing the reinfection focus. Also, a few observations on older tuberculous complexes of different structural age were added (paper X), and in 2 of these the histological analysis of all tuberculous foci in the lungs and in the corresponding lymph nodes, found in various stages of regression, suggested the possibility of three different periods of exogenous infection. Anatomical findings of a recent intestinal reinfection complex were incidentally discovered in one case, that of a young Negress who had died in uremic coma of diffuse glomerulonephritis (paper IX). It also was shown (paper VIII) that the reinfection complex can furnish the source for progressive fatal tuberculosis by more or less protracted hematogenous spread. This serious complication, however, was present only in 2 cases out of a total of 29, all of which formed the basis of our previous reports on the reinfection complex.

The scarce notes in the literature (Hesse, Schuermann and Anders) referring to postmortem findings of a recent reinfection simulating a typical primary complex have been quoted in our paper on pulmonary complexes of different age (VII). It was mentioned that, in a systematic study of 1,000 cases by Schuermann (2), 2 instances were included with stony remnants of an old primary pulmonary complex and anatomical findings in the intestinal tract and the mesenteric or mesocolic lymph nodes representing the less old and still active complex of intestinal reinfection. The ages in these 2 cases were sixty-two and seventy-three years. In both there were additional tuberculous lesions

[1] From the Department of Pathology, Medical School, University of Buffalo, and the Pathology Laboratories of the General Hospital and Children's Hospital, Buffalo, New York.

found: in kidney, epididymis and spleen in one, and in liver and angulus lymph nodes in the other. All these additional tuberculous changes were considered by Schuermann to be lympho-hematogenous metastases from the intestinal reinfection complex. After describing the anatomical findings Schuermann stated, "I would not dare to explain this case in such a manner were it not for the picture of a complete primary complex in the intestine [a healing tuberculous ulcer in the cecum and several small ulcers in the lower ileum with older caseated lesions in the mesenteric lymph nodes] and also for the fact that the old and the more recent primary complex are in 2 organs with entirely separate lymphatic drainage." It is apparent from the wording of this statement how deeply experienced students of the pathology of tuberculosis were impressed by an almost dogmatic belief that whatever conformed to the typical picture of a primary complex (Ranke) in the lungs or in the intestinal tract was considered the anatomical substrate of the first infection only.

In another paper dealing with the primary complex in its relation to the various anatomical pictures of tuberculosis, which was published two years previously (3), Schuermann already had mentioned that in 9 cases out of 1,000 a recent complex with or without generalized tuberculosis was seen postmortem in the presence of an old primary complex with stony or ossified foci. In one of these the anatomical findings were given very completely. In all cases both complexes were in different organ systems, the recent in the intestine, the older in the lung. They were found in 6 cases between fifty-one and sixty-five, and in the remaining 3 between sixty-six and eighty years. A few "questionable" cases were mentioned also in which the more recent and older changes were found only in the lungs. No further detail was given, however, on these findings, including the remaining 8 cases with the apparently recent intestinal reinfection complex, at that time. In referring to caseated or fibrocaseated lesions in primary complex-like arrangement, in cases beyond fifty or sixty years of age, Schuermann felt they should be suspected to be true reinfections, that apart from this recent complex another one with completely healed stony-ossified foci might be present. He seemed reluctant to admit that a true reinfection complex might occur also in younger age groups, because all the 9 cases with an intestinal reinfection complex were seen only beyond fifty years of age. He therefore postulated that it takes about fifty years to complete the cycle of reactions (*Reaktionszyklus*) initiated by the primary infection, if acquired during childhood. He was aware that such a theory represented a *petitio principii* until further observations might shed more light on this issue. Schuermann stated that he was planning to deal exclusively with these findings in a special paper. To my knowledge no further report was ever published by Schuermann on these matters, apart from a brief reference to 2 different cases observed a few years later, which I quoted above (2). At that time he seemed even more inclined to recognize a true reinfection complex, only when observed in a different organ system from that in which the remnants of the primary complex are present. This cautious attitude, I believe, was conditioned largely by the great weight

which the views on "endogenous lymphoglandular reinfection" carried at that time.

It is evident from these reports that Schuermann not only had carefully observed and analyzed the recent reinfection complexes in the intestinal tract, but that he apparently had seen also Ranke complexes of different age in the lungs, although he called these latter findings "questionable." Unfortunately we never shall learn more of Schuermann's original observations to which we felt obligated to refer in some detail, as this outstanding tuberculosis pathologist has fallen victim to the war.

In the last five years in the continuation of our systematic morphological studies on the pathogenesis of tuberculosis in man, it was no surprise to discover a good number of additional cases with a reinfection complex. Such findings, we feel, should be considered no longer as an occurrence of great rarity. They are listed in table 1, arranged according to age. We have included in this paper 29 cases. The presence of the reinfection complex is the main issue, as in 7 cases of this series, just as in 8 cases previously reported (XI) there was no corresponding lymph node change to the old primary focus. The complex of the recent reinfection, however, was fully established in these cases, with considerable caseation of the lymph nodes regional to the reinfection focus. This series contains also 2 cases with hematogenous tuberculous disease caused by the lesions of the reinfection complex. We have selected 7 cases for illustration. The anatomical findings of these will be given in some detail. The table contains the pertinent findings in all cases of this series.

In the photographic illustrations very low magnifications (ranging about between 4 and 8×) are used. As the size of the focal lesions in the lungs is given in millimeters, the magnification can be readily measured by the reader. They are consistent in each case unless otherwise indicated. In those cases in which the roentgenograms taken postmortem are shown, it is indicated on the attached outline which are the primary and reinfection complexes. In all cases in which these outlines are used, the lettering uniformly refers to the components of the primary complex and of the reinfection complex: PF indicates primary focus; PL, lymph nodes regional to the primary focus; RF, reinfection focus; RL, lymph nodes regional to the reinfection focus.

It was planned to show the roentgenograms of every case selected for illustration. The only reason why we decided to omit most of them was the presence of a few firmly calcified structures in various parts of the lungs of nontuberculous nature, which in the photograph alone, without the accompanying histological pictures, are apt to complicate an otherwise clear and comparatively simple issue. We have indicated in the table the location and nature of these small calcified structures which, without histological examination, would be mistaken for calcified tuberculous lesions. I would have preferred to show the microphotographs along with the postmortem roentenograms of every single case contained in the table. In all, the structural distinctions are very clear and most —if not all—of them could be used as typical examples of a reinfection complex.

TABLE 1

Anatomical findings in 20 cases with reinfection complex

CASE NUMBER	AGE, RACE, SEX	PRIMARY COMPLEX		REINFECTION COMPLEX		ADDITIONAL FINDINGS, INCLUDING HEMATOGENOUS TUBERCLES AND LESIONS FROM FOCAL EXTENSION
		Primary Focus	Regional Lymph Node Changes	Reinfection focus	Regional Lymph Node Changes	
E 60	24, White M	Midportion left upper, 1.5 mm., stony with incomplete bony shell	Regional left bronchopulmonary lymph nodes, firm stones	Centre right middle, 8 x 5 mm., chalky-caseated, in part calcified	Regional bronchopulmonary and right lower tracheobronchial lymph *nodes*, extensive chalky-fibrous changes with central calcification	Scattered *fibrocaseated* miliary tubercles in both lungs, 1 mm. or less in diameter, *in liver* and spleen
E 104	24, White F	2—lower third right upper, 2 x 1.2 mm., stony-ossified with firm *fibrous encapsulation*; upper third left upper, 1 mm., stony-ossified		Right middle, 5 mm., caseated-chalky	Right lower tracheobronchial and pretracheal lymph *nodes*, extensive caseated-chalky lesions with central calcification	
CH 1202	26, White F	Hilar level left upper, 1 mm., stony-ossified		Right middle, 2 x 2.5 mm., firmly caseated	Right interlobar bronchopulmonary lymph nodes, firmly caseated	A few minute subpleural tubercles around reinfection focus, with dust-like chalky impregnation of caseated core
4080	27, White F	2—lower part left upper, 2 mm., stony-ossified. No old focus found in right lung; firm adhesions between right middle and lower lobes	Right lower and left upper tracheobronchial lymph nodes, firm stones with considerable ossification in the latter	Base left lower, 6 mm., caseated	Left lower tracheobronchial and anterior mediastinal lymph nodes, caseated	Focal extension to right middle from reinfection focus. Tuberculous pleuritis around left lower, in organization
4628	36, White F	Not found	Left bronchopulmonary lymph node, firm stone	Right middle, 4 x 5 mm., caseated	Regional subpleural, interlobar, lower and upper tracheobronchial *lymph* nodes, caseated, with epithelioid cell tubercles	

2170	38, White M	Apex left lower, 1.5 x 1 mm., firm, stony-ossified		Middle third left lower, 3 x 1.5 mm., fibrocaseated. One small satellite tubercle	Regional subpleural, interlobar, bronchopulmonary and lower tracheobronchial lymph nodes, cheesy-fibrous conglomerate tubercles	Anthracosilicotic nodule with central calcification in right upper
4670	40, White M	Upper third left upper, 1 mm., calcified	Same level, 1 mm , hyaline intrapulmonary nodule in parenchyma	Middle third right upper, 10 x 13 mm., caseated	All regional bronchopulmonary and upper tracheobronchial lymph nodes, caseated	Osteoma, right upper. Calcified anthracosilicotic subpleural lymph nodule, right middle
4680	49, White F	Upper third right lower, 3 x 4 mm., calcified-bony	Regional bronchopulmonary lymph nodes, stony-ossified	Lower third left upper, 10 x 7 mm., caseated-fibrous, with regional subpleural tuberculous lymphangitis	Regional bronchopulmonary and anterior mediastinal lymph nodes, caseated	Scattered recent miliary tubercles in lungs, liver, spleen, kidneys Several minute osteomata, right lower
5131	50, White F	Hilar level right upper, 1 mm., firmly petrified	Regional bronchopulmonary and upper tracheobronchial lymph nodes, firm stones	Subapical, left upper, 7 x 8 mm., firmly caseated, with central cavitation	Regional bronchopulmonary and upper tracheobronchial lymph nodes, caseated conglomerate tubercles	Recent minimal focal extension to left apex from reinfection focus. Osteoma, apex left lower. Phlebolith, apex right upper. A few fibrous miliary tubercles in liver and spleen
4932	54, White F	Centre right middle, 3 x 2 mm., stony-ossified	Regional subpleural lymph nodule and bronchopulmonary lymph nodes, ossified	Midportion left lower, 10 mm., caseated	Regional bronchopulmonary, lower and upper tracheobronchial and anterior mediastinal lymph nodes, extensive caseation	Perifocal, intrabronchial spread around reinfection focus, with a few large satellite tubercles. A few small fibrous-cheesy tubercles in liver and spleen
4126	54, White F	Lower third right upper, 2 x 2 2 mm., ossified		Base right lower, 11 x 8 mm., cheesy	Right bronchopulmonary and right lower tracheobronchial lymph nodes, chalky-caseated — extensive changes	
5123	56, White M	Right middle, minute white shadow on X-ray, 1 mm. Focus not found	Right bronchopulmonary and lower tracheobronchial lymph nodes, firm stones	Base left lower, 7 x 5 mm., firmly caseated	Regional left bronchopulmonary, lower tracheobronchial and pulmonary ligament, extensive caseation with slight chalky changes	Ossified-stony focus, 1 mm., apex left upper, apparently old focal extension from primary complex. Osteoma, 2 x 3 mm., base right lower—mistaken for primary focus

TABLE 1—*Continued*

CASE NUMBER	AGE, RACE, SEX	PRIMARY COMPLEX		REINFECTION COMPLEX		ADDITIONAL FINDINGS, INCLUDING HEMATOGENOUS TUBERCLES AND LESIONS FROM FOCAL EXTENSION
		Primary Focus	Regional Lymph Node Changes	Reinfection focus	Regional Lymph Node Changes	
4335	58, White M	Apex right lower, 2.2 mm., ossified	2 regional minute hyaline-calcified subpleural tubercles. Regional bronchopulmonary lymph nodes, firm stones	Base left lower, 15 x 11 mm., caseated	Left lower tracheobronchial lymph nodes, diffuse caseation	Minute calcified anthracosilicotic nodule in left apex
4839	58, White M	Middle third left lower, 10 x 7 mm., ossified	Left lower tracheobronchial lymph nodes, firm stones	Base right lower, 13 x 15 mm., chalky-fibrocaseated	Right lower tracheobronchial lymph nodes, chalky-caseated	
5208	59, White F	Midportion right upper, 1 mm., ossified	Right upper tracheobronchial lymph nodes, calcified stones	Midportion left upper, 22 x 20 mm., soft, caseated, with a few satellite tubercles	Left upper tracheobronchial and anterior mediastinal lymph nodes, soft, caseated	Scattered soft hematogenous tubercles, both lungs, liver, spleen, from reinfection complex
E 124	59, Colored M	Lower third left upper, 4 x 3 mm., firm stone surrounded by a bony shell	Regional left bronchopulmonary and lower tracheobronchial lymph nodes, extending into the right lower group, very firm stones encased in hyaline tissue	Lower third right upper, 6 x 5 mm., chalky-fibrocalcified with considerable cholesterol debris	Regional bronchopulmonary and upper tracheobronchial lymph nodes, diffuse chalky-calcified conglomerate tubercles	
5301	60, White M	Upper third right upper, 3 mm., calcified-ossified	Anterior bronchopulmonary and upper tracheobronchial lymph nodes, firm stones	Hilar level right upper, 20 x 25 mm., firmly caseated	Entire regional lymph node chain, including right angulus lymph nodes, diffuse caseation	Local focal extension to right upper, right middle and lingula of left upper from reinfection focus. Calcified anthracosilicotic nodule, 2 mm., left subapical field. A few scattered fibrocaseated miliary tubercles in liver and spleen

4587	61, White M	Middle third right upper, 5 x 4 mm., ossified	Right bronchopulmonary and right lower tracheobronchial lymph nodes, ossified-stony	Upper third left upper, 6 x 4 mm., fibrocalcified, with little bone formation	1 regional bronchopulmonary group, fibrocalcified	Structural age difference distinct only in lymph nodes. 2 calcified anthracosilicotic subpleural lymph nodules in right lower. Adhesions around right lung
5256	66, White M	Subapical field left upper, 3 mm., ossified-stony	Regional bronchopulmonary lymph nodes, firm stones	Subapical field right upper, 8 x 7 mm., caseated, central cavity	Right paratracheal lymph nodes, caseated conglomerated tubercles	Single focal extension to left apex from old focus. Several osteomata in left lower, also 1 phlebolith
2345	64, White M	Lower third right upper, 2.5 x 2 mm., firmly ossified stone		Right subapical portion, 7 mm., chalky-caseated with central disintegration	Right upper and lower tracheobronchial lymph nodes, cheesy-chalky and slightly calcified lesions	Focal extension to left lower from reinfection focus. Minute osteoma in right middle
4598	67, White M	2—hilar level left upper, 2 x 1.5 mm., 2 x 1.4 mm., ossified	Left bronchopulmonary lymph nodes, firmly stony	Upper third left upper, several fibrous-cheesy foci with minimal chalk, about 4 x 5 mm., each. Single focus right middle, about 10 x 20 mm., firmly caseated	Left upper tracheobronchial and right bronchopulmonary lymph nodes, caseated (2 reinfection complexes)	Caseated subpleural lymph node at mediastinal surface of right upper. Few recent miliary tubercles in spleen and liver
4289	68, White F	Middle third left upper, 2 x 1.8 mm., ossified	Left bronchopulmonary lymph nodes, firm small stones and hyalinized conglomerate tubercles	Right middle, 18 x 12 mm., firmly caseated, with minimal chalky changes	Right bronchopulmonary lymph nodes, firmly caseated	2 pinhead sized osteomata, midportion right upper. Calcified anthracosilicotic nodule in bronchopulmonary lymph node of primary complex area; another in left upper
4701	71, White F	Middle third right upper, 2 x 1.5 mm., firmly ossified	1 regional upper tracheobronchial lymph node, small stones	Upper third left upper, 5 x 4.5 mm., chalky-calcified	1 regional bronchopulmonary lymph node, chalky-fibrocalcified	
4621	74, White F	Upper third left upper, 1 x 1.5 mm., ossified. 3—lower third right upper, 1 x 1.2 mm., 1 x 1.3 mm., 2.5 x 2 mm., stony		2—lower third left lower, 5 x 6 mm., 4 x 3 mm., cheesy-chalky	Regional bronchopulmonary lymph nodes, cheesy-chalky with central disintegration	Localized focal extension to left upper and left lower from reinfection foci. Scattered hematogenous tubercles in spleen, liver (chalky-fibrous)

TABLE 1—*Concluded*

CASE NUMBER	AGE, RACE, SEX	PRIMARY COMPLEX: Primary Focus	PRIMARY COMPLEX: Regional Lymph Node Changes	REINFECTION COMPLEX: Reinfection focus	REINFECTION COMPLEX: Regional Lymph Node Changes	ADDITIONAL FINDINGS, INCLUDING HEMATOGENOUS TUBERCLES AND LESIONS FROM FOCAL EXTENSION
4230	75, White M	2—lower part right middle, 3 x 2.5 mm.; middle third left upper, 3 mm.; stony-ossified	Left and right bronchopulmonary lymph nodes, small fragmented stones	Hilar level left upper, 12 x 11 mm., firm, chalky-fibrous	Left upper tracheobronchial lymph nodes, chalky-caseated	Combined with calcified anthracosilicosis in bronchopulmonary lymph nodes on both sides
5207	77, White F	Base left lower 4 x 3 mm., firmly ossified		Middle third left upper, 10 x 13 mm., extensively caseated	Left upper tracheobronchial, bronchopulmonary and paratracheal lymph nodes, caseation, with small central cavities	Scattered hematogenous fibrous-cheesy tubercles in both lungs, spleen, liver, kidneys, myocardium, from the reinfection complex. 5 anthracosilicotic nodules—left apex and right middle
E 6	79, White M	Upper third right lower, 3 x 3.5 mm., firmly ossified	Right bronchopulmonary, lower and upper tracheobronchial lymph nodes, firm stones	Midportion left upper, 8 x 7 mm., fibrocaseated	Left bronchopulmonary, lower and upper tracheobronchial lymph nodes, diffuse fibrocaseous lesions	Combined with calcified anthracosilicosis in several bronchopulmonary and lower tracheobronchial lymph nodes
			Active Progressive Tuberculosis from Focus of Reinfection			
5007	41, Colored F	Middle third right upper, 4 x 2 mm., firmly calcified with fibrous capsule	2 right upper tracheobronchial lymph nodes, fibro-calcified	Lingula of left upper, 7 x 6 mm., consisting of 2 individual lesions, soft, caseated	Left lower tracheobronchial lymph nodes, diffuse soft caseation	Tuberculous pleuritis, left lung. Miliary tuberculosis. Tuberculous meningitis
5306	57, White M	2—upper third left upper and upper third left lower, about 2 x 1 mm., each; former calcified-ossified, latter firm stone	Bronchopulmonary lymph nodes regional to left upper and left lower lobes, calcified	Middle third left lower, 10 x 9 mm., caseated	Regional lower tracheobronchial lymph nodes, fibro-caseated	Hematogenous spread in spleen, liver, adrenals, tongue, with extensive caseation of both adrenals and tuberculoma of tongue. Calcified anthracosilicotic nodule in right upper

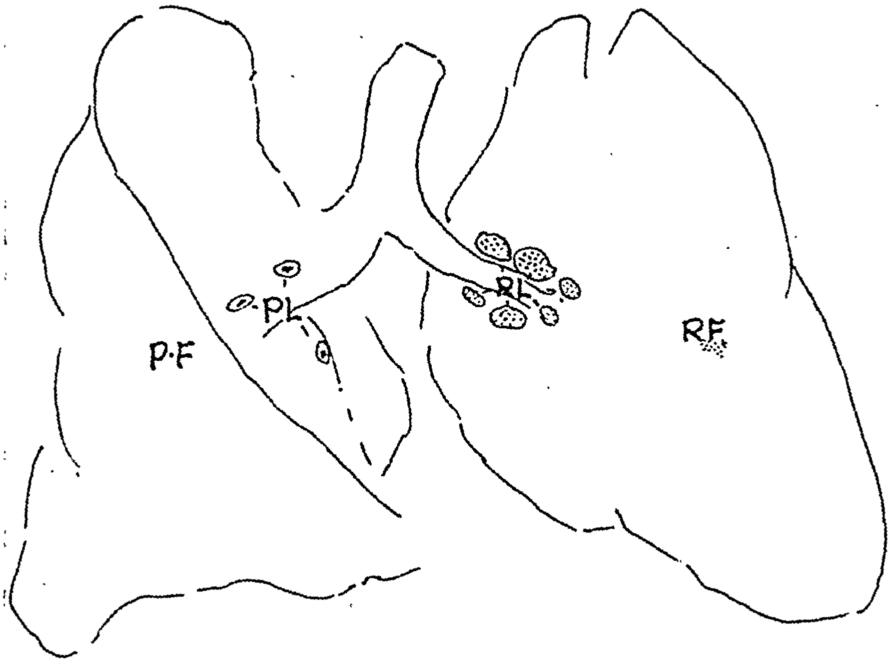


PLATE 1a

PLATES 1a and b. PF—Firm stony primary focus in the right middle lobe with complete osseous shell. PL—Bronchopulmonary lymph node regional to the primary focus, containing a firm stone surrounded by bone tissue with lymphoid marrow. RF—Reinfection focus in the midportion of the left lower lobe, firmly caseated, with two satellite tubercles at the left lower border. RL—One of the bronchopulmonary lymph nodes regional to the reinfection focus with confluent caseated conglomerate tubercles. The calcified primary complex is clearly seen on the X-ray film. Part of the density about the hilum of the left lung is caused by the caseated bronchopulmonary and lower tracheobronchial lymph nodes regional to the reinfection focus.

tracheobronchial and in the anterior mediastinal group were very soft. This reinfection focus, as seen in the photograph, showed two small atelectatic areas entirely included in

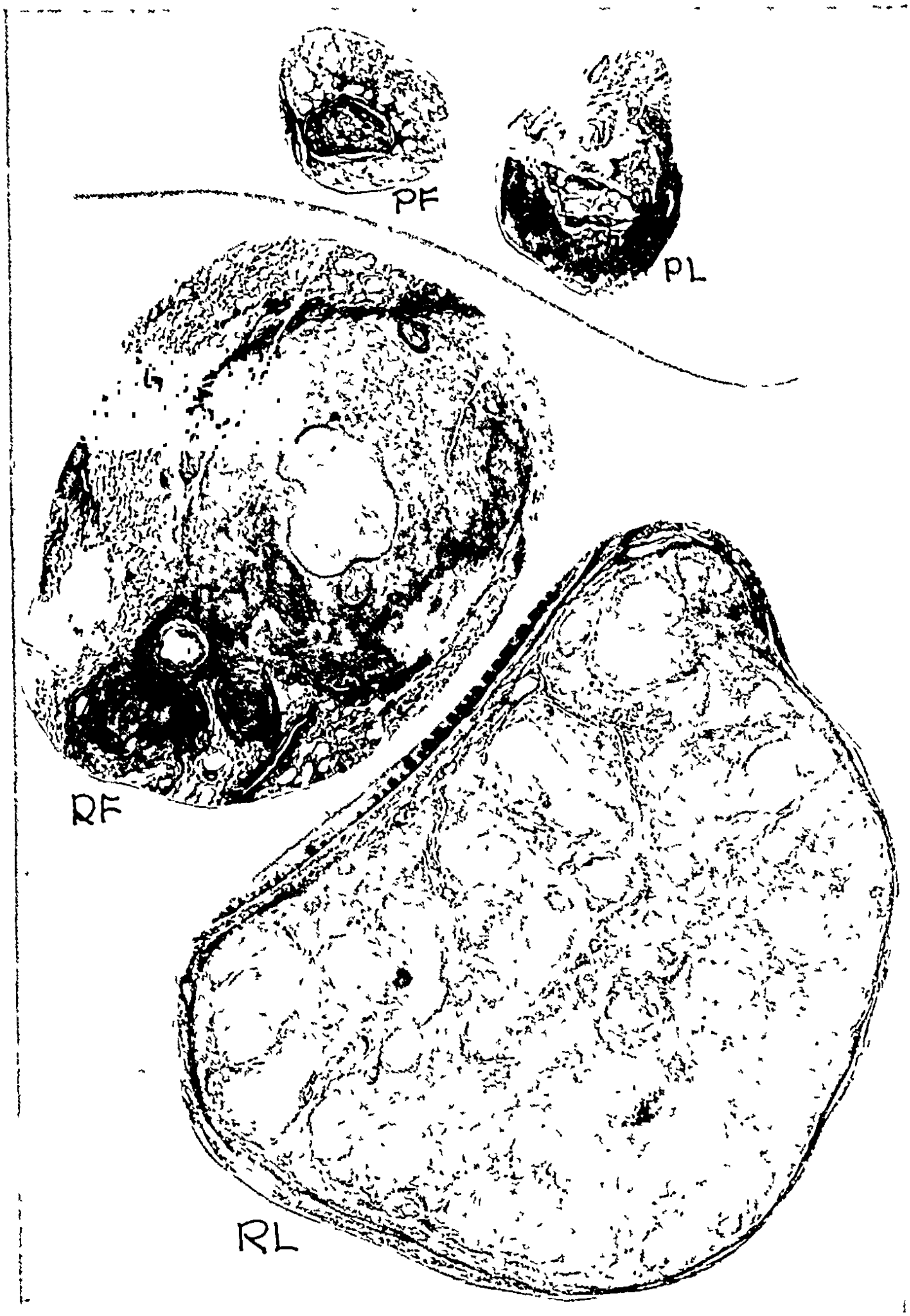


Plate 1b

the massively caseated lung tissue. There were no tuberculous lesions within the small atelectatic islands. A few finger-like protrusions about the capsule pointed to the way of

PLATE 2. The primary focus in firmly ossified state and the small stony conglomerate tubercles in its regional bronchopulmonary lymph node are shown in the corresponding field of the right upper lobe. The reinfection focus with one of several caseated regional lymph nodes are seen in the corresponding field of the left lung. Note the large size of the diffusely caseated reinfection focus, with a few satellite tubercles to the left and two atelectatic, non-caseated areas near the more central portions, with considerable disintegration of the cheesy matter. Note also considerable disintegration in the diffusely caseated bronchopulmonary lymph node regional to the reinfection focus.

PLATE 3. The primary focus in firm, stony state and in hyaline encapsulation, with a stony tubercle in one regional bronchopulmonary lymph node, is shown in the corresponding area of the right lung. The reinfection focus in the left subapical field shows diffuse caseation and considerable disintegration with beginning cavitation. Note the large confluent caseated tubercles in one of the regional bronchopulmonary lymph nodes. Below and lateral to the reinfection focus is a typical "osteoma."

extension, which had led to an unusually large size in this reinfection lesion. It most probably had formed from gradual fusion of several smaller bronchial tubercles in typical acinous arrangement. In this case there was scattered hematogenous seeding, especially in the liver and spleen, but also in both lungs, in which a few tubercles were found in the subpleural areas on both sides. Although they felt fairly firm to the palpating finger, they did not show any calcification on the X-ray photograph and proved to be small caseated tubercles in fibrous organization. The postmortem roentgenogram shows a very distinct soft whitish shadow in the area of the reinfection focus; the extensive caseation in the left upper tracheobronchial and mediastinal lymph nodes is also very distinct. In addition, the minute stony fragments in the lymph nodes regional to the primary focus, itself, are very clearly seen.

Just as there is occasionally, in primary lesions, no compact contiguous caseation, an outwardly large reinfection focus might include a few atelectatic areas free of actual tuberculous changes.

Case 3: (B. G. H. 5131) Fifty year old white male. Cause of death: uremia from progressive arteriolar sclerosis of the kidneys. (See plate 3)

This is a very typical case, with two complexes of different age. The primary complex consists of a single primary focus at the hilar level of the right lung, in the right upper lobe near the interlobar fissure.[2] Histologically there is a firm stone within a thick hyaline capsule, but without bone formation. In the regional right bronchopulmonary and upper tracheobronchial lymph nodes there are several small stony particles. The reinfection complex is formed by a well encapsulated, cheesy focus, 6 x 7 mm. in diameter, with beginning cavitation, in the infraclavicular area of the left upper lobe, with localized adhesions to the pleura, and by diffusely caseated confluent conglomerate tubercles in the regional bronchopulmonary and upper tracheobronchial lymph nodes. The photograph of the reinfection focus very clearly shows its disintegration, the encapsulation by a thin fibrous wall, and—to the left in the picture—localized perifocal spread apparently within a smaller bronchus.

Again, the postmortem X-ray photograph showed a few additional calcified structures. There was a round whitish shadow in the apical portion of the left lower lobe, distinctly larger than that of the primary focus in the opposite lung. This, however, proved to be a typical "osteoma." Two other shadow-giving lesions, not indicated on the chart, were a typical phlebolith in the subapical field of the left upper lobe and a minute hyalinized nodule with a caseated core, with minimal central chalky changes, in the left apex, caused by focal extension from the reinfection focus.

There were a few blood-borne fibrous tubercles of miliary size in liver and spleen, in connection with the reinfection.

Case 4: (B. G. H. 4839) Fifty-eight year old white male. Cause of death: carcinoma of the stomach. (See plates 4a and 4b)

In this case the reinfection complex has already reached an advanced state of firmly caseated-chalky regression. The difference in the structural age, however, is considerable, as can be seen from the microphotographs of the lesions composing primary complex and reinfection complex. The primary complex is represented by a mostly ossified focus, 10 x 7 mm., in the middle third of the left lower lobe, and by a few entirely petrified lymph

[2] On the diagram shown on plate 3 this focus should have been placed somewhat above the level depicted, close to the fissure between middle and upper lobe.

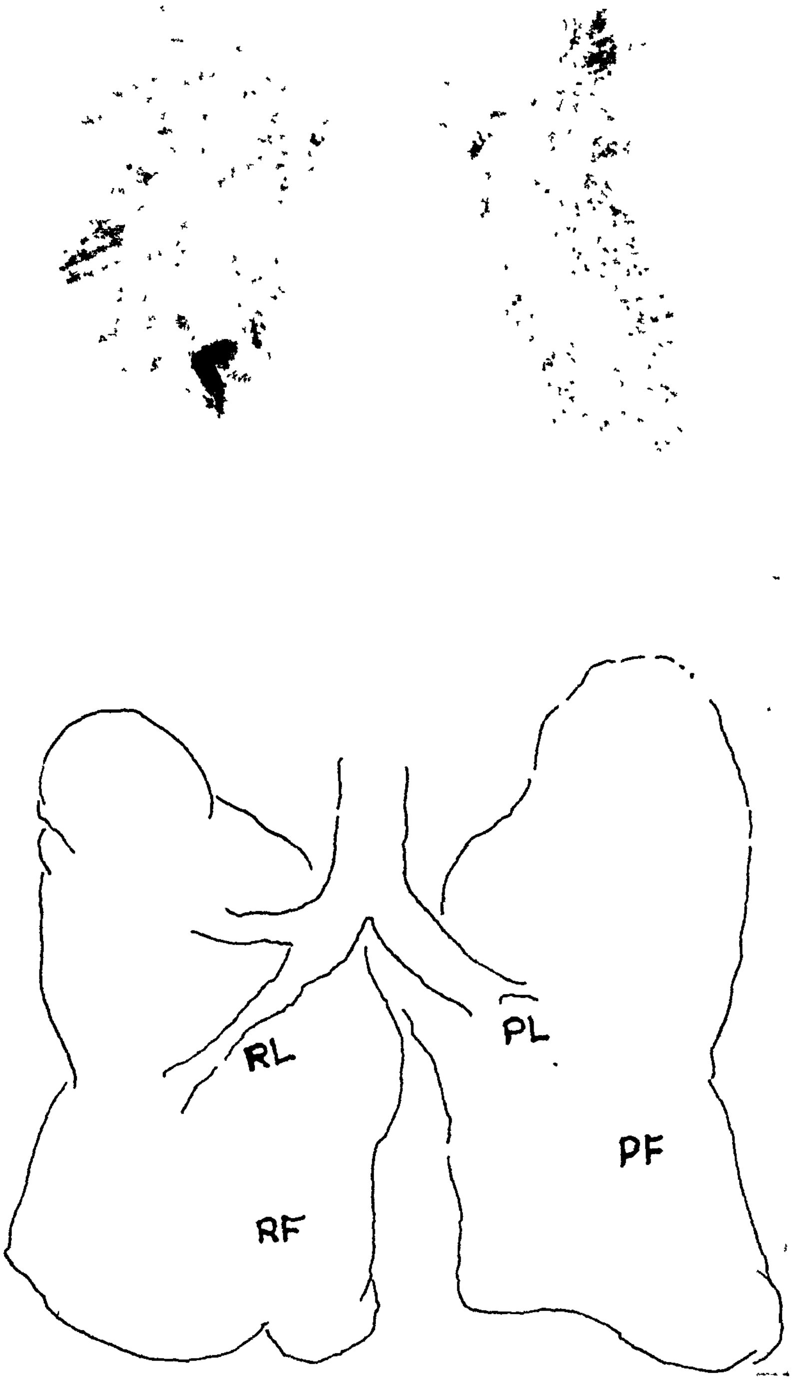


PLATE 4a

PLATES 4a and b. PF—Primary focus in stony-ossified state with very much bone marrow. PL—A regional bronchopulmonary lymph node in stony-ossified state with some marrow. RF—Reinfection focus firmly encapsulated, in diffuse chalky state. RL—Lower tracheobronchial lymph node regional to the reinfection focus, chalky-caseated with active tuberculous granulation tissue.

nodes of the left lower tracheobronchial group and between left upper and lower lobe. The histological picture of the primary focus shows an unusual size. Not only is the

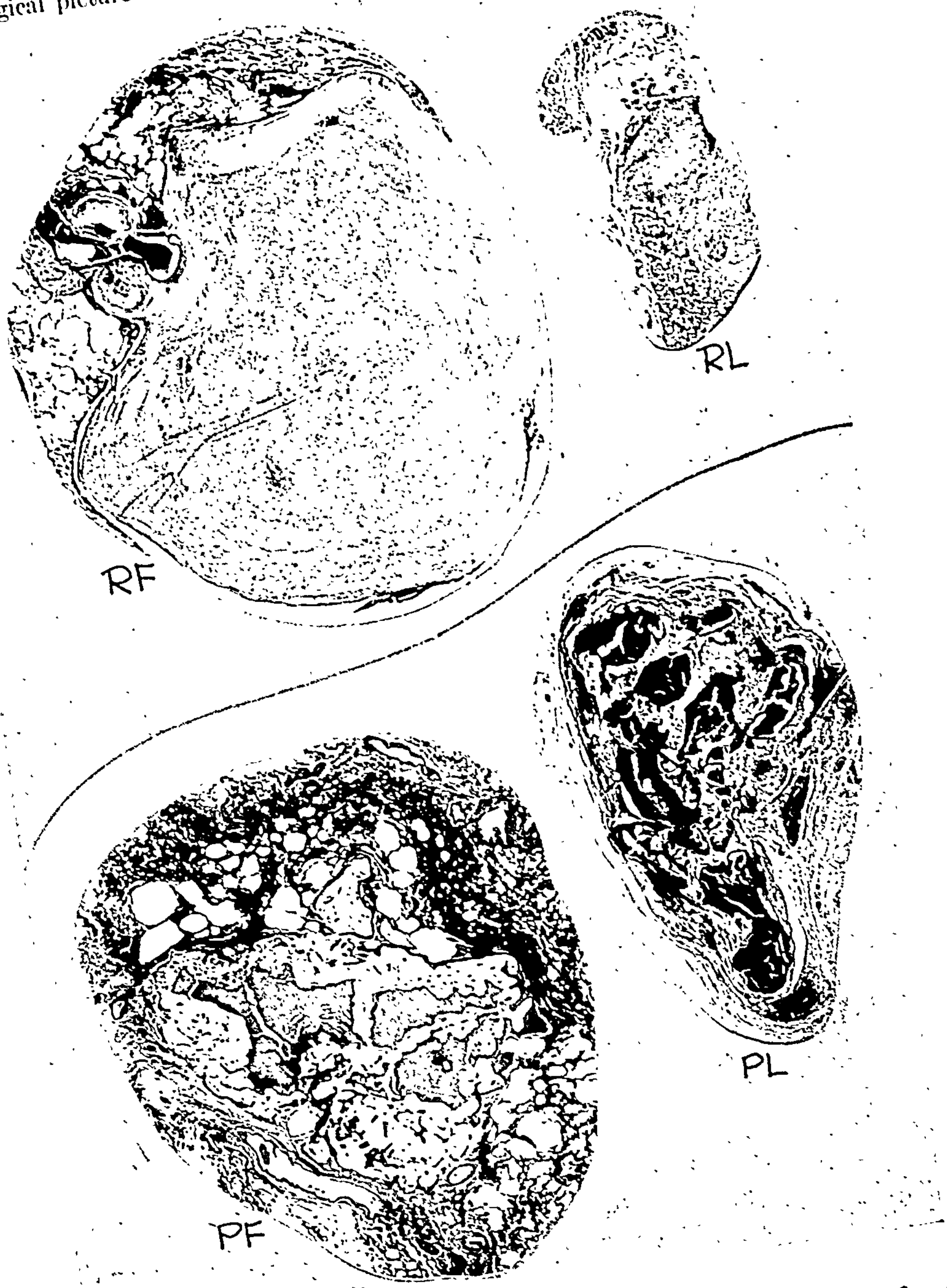


Plate 4b

entire lesion surrounded by a thin, bony shell, but also what still remained of the firm calcified matter in the core of the lesion, split up into various fragments, is for the most part

surrounded by bone tissue. There is a great deal of bone marrow, mostly fat marrow, but here and there containing a moderate number of lymphoid cell between fine capillaries, and anthracotic pigment. The original pneumonic alveolar pattern within the firmly stony core is faintly noticeable in the hematoxylin-eosin section. The histological picture in the lymph nodes of the old primary complex is not less-impressive. We see comparatively large particles of stony matter, here and there with irregular marginal bone formation, or in granular and globular fragmentation. There are hyalinized collagenous and edematous fat tissue and masses of lymphoid cells forming a marrow-like structure between the larger stony fragments. Some of these are still entirely encapsulated by collagenous walls. The smaller ones are in an advanced process of fragmentation and resorption.

The reinfection complex consists of a focus, 13 x 15 mm., in firm chalky fibrocaseated state, in the basal portion of the right lower lobe, and of conglomerated chalky-caseated tubercles in the right lower tracheobronchial lymph nodes. Although the X-ray photograph gives a rather compact whitish shadow of the reinfection focus, it still was soft enough to be cut with the knife. The X-ray photograph of the primary complex and reinfection complex would hardly suggest such a great difference in their structural age as the microphotographs disclose. All we see is a very firm, caseated-chalky lesion, well encapsulated by a collagenous, mostly hyalinized wall. Again, there is very limited perifocal extension forming a few satellite tubercles around a branch of the pulmonary artery, which bulges somewhat into the capsule of the reinfection focus. Similarly, all sections taken through the right lower tracheobronchial lymph nodes draining the area of the reinfection focus show large conglomerated caseated-chalky tubercles, with active tuberculous granulations (epithelioid cell tubercles and many Langhans' giant cells) bordering especially the disintegrated central areas, while the capsules of the larger conglomerate tubercles show considerable hyalinization. In this case there was no evidence of any hematogenous spread from the lungs. It should be considered as a "model case" of tuberculous complexes of different age with the reinfection complex in an already advanced fibrocaseated and diffusely chalky state. That the X-ray photographs of such lesions might not always disclose the real extent of structural age difference can be realized from a comparison of the whitish shadows in the right lung, which appear unusually compact—as seen in diffusely calcified lesions—with those in the left lung where, especially in the shadow indicating the primary focus, the fragmentation and disintegration and the irregularity of the opaque whitish areas are suggestive of considerable bone formation with intervening bone marrow. Also, it is of interest in this case that there is a certain degree of symmetry of primary and reinfection complex regarding site and size of the focal lesion and the extent of the lymphogenous progression. Naturally, later regressive stages would have reduced the size of the reinfection lesion. Findings of this nature, which so far were rare chance observations, might suggest that a true reinfection will produce a lesion similar in size and extent to the first infection, provided the resistance of the host tissue has not changed. Also, these calcified and chalky lesions, when seen on the chest film of a patient, especially if accompanied by corresponding calcifications at the hilum of each lung, are apt to be misinterpreted as multiple primary complexes rather than recognized as complexes of different age.

Case 5: (B. G. H. 5301) Sixty year old white male. Cause of death: Hodgkin's disease of retroperitoneal lymph nodes and spleen. (See plate 5)

In this case both the primary and reinfection focus are in the same lobe (right upper). In some of the lymph nodes draining this lobe we find old and recent changes together, as indicated in the photograph. It shows caseated conglomerate tubercles throughout most

of the node, but in one part—to the left in the photograph—there is a firmly encapsulated stone which does not seem to merge with the surrounding caseated structures. Also, in a few upper tracheobronchial lymph nodes with extensive changes from the old primary infection, consisting of well encapsulated small stones, there are a few recent fibrocaseated tubercles in the centre and—to the right in the photograph—between and around the firm stones. The primary focus, located in the lateral upper field, is 3 mm. in diameter, in firmly petrified and partly ossified state, with a complete bony shell and irregular scar tissue about the lesion (along the upper border of the focus in the photograph). A few bronchopulmonary lymph nodes in front of the bronchus draining the right upper lobe, and two upper tracheobronchial lymph nodes show extensive calcification. In the histological picture these nodes contain completely encapsulated stones and a few fibrocaseated conglomerate tubercles, obviously secondary to the reinfection focus.

The reinfection complex is formed by an unusually large, firmly caseated focus, 20 x 25 mm., at the upper hilar level in the lateral portion of the right upper lobe. The lymph node changes regional to this lesion include the bronchopulmonary, upper tracheobronchial, paratracheal and angulus lymph nodes of the same side. They all show diffuse caseation in the histological picture: relatively recent caseated conglomerate tubercles without hyalinization. There are also a few fibrocaseated tubercles in the central-most bronchopulmonary lymph nodes regional to the reinfection focus. The lymph nodes of the venous angle, in particular, contain diffusely caseated conglomerate tubercles with but little fibrosis. The histological picture of the reinfection focus (magnified about 4 to 5X) shows a caseated tuberculoma in distinct encapsulation with very early chalky changes and with a rare satellite tubercle around the focus. In the X-ray photograph it appeared as an opaque grayish shadow, not suggestive of any calcification. There were, in addition —not visible on the X-ray film—a few fibrocaseated tubercles with central chalky changes, about 2 mm. in diameter, in the subapical portion of the right upper lobe, in the lingula of the left upper lobe and in the right middle lobe. All of these were, in the histological picture, firmly encapsulated fibrocaseated tubercles with minimal central chalky changes. One distinctly calcified nodule in the left subapical field proved to be a calcified anthracosilicotic structure.

All lesions, including all lymph nodes draining the right lung, were examined in this case; also every small shadow-giving structure seen on the X-ray photograph. In contradistinction to the 4 cases previously presented, in this case some of the lymph nodes draining the right upper lobe contained both old and recent changes. But, just as in some of our cases reported previously in a paper dealing with progressive reinfection, it is evident from the entire anatomical analysis that old and recent lymph node changes belong to the two entirely different periods of first and reinfection. The firm encapsulation of the stony tubercles in the few lymph nodes regional to the obsolete primary focus speaks against any possibility of so-called endogenous exacerbation. There was but restricted focal extension forming a few small fibrocaseated tubercles with minimal chalky changes; and, in addition, hematogenous spread to liver and spleen, with a few scattered fibrocaseated miliary tubercles.

Case 6: (B. G. H. 5207) Seventy-seven year old white female. Cause of death: generalized atherosclerosis, pontine hemorrhage, pneumonia. (See plate 6)

In this case only the anatomical picture of the reinfection complex was very clear at gross inspection. The postmortem X-ray film showed four firmly calcified small nodular structures between 3 and 5 mm. in thickness, in right middle and lower lobes; and three more in the subapical portion of the left upper lobe. Finally, there was a single calcified structure in the base of the left lower lobe. To none of these, however, was there any

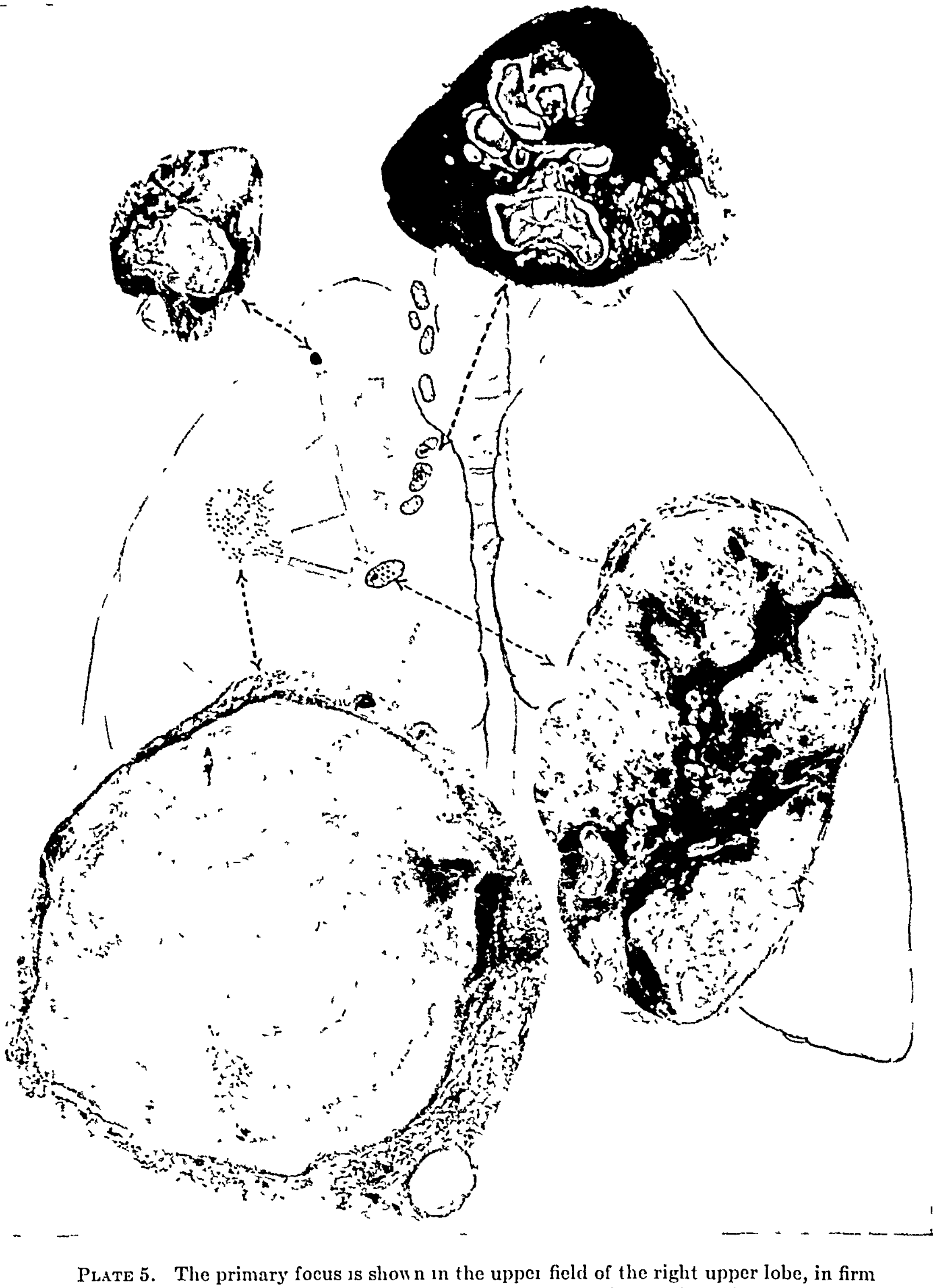


PLATE 5. The primary focus is shown in the upper field of the right upper lobe, in firm stony, partly ossified state, surrounded by scar tissue. The large reinfection focus in the lower lateral part of the same lobe. Note the presence of firmly encapsulated stony tubercles along with recent caseated tubercles in one of the lymph nodes regional to the primary focus (upper field), and the diffuse caseation with one small encapsulated stone in one bronchopulmonary lymph node regional to the reinfection focus (lower field).

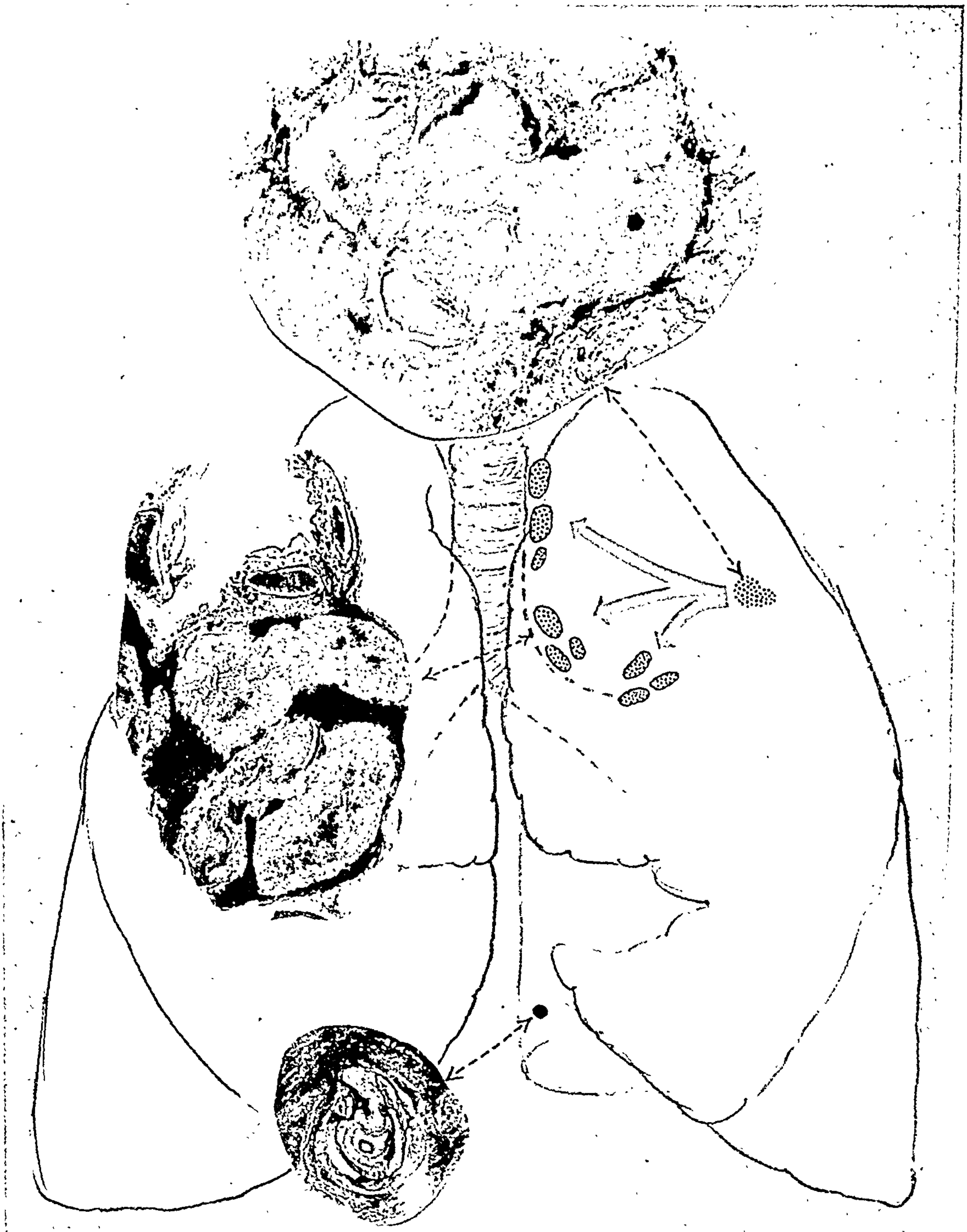


PLATE 6. The primary focus (without corresponding lymph node changes) is shown in the lower field of the left lung, in firmly stony-ossified state. The reinfection focus is in the upper field of the left lung, in soft, caseated, disintegrating state. Note also the diffuse caseation in one of the bronchopulmonary lymph nodes regional to the reinfection focus.

corresponding lymph node lesion seen, neither on the X-ray film nor at gross dissection. It was felt previous to histological analysis that we were most probably dealing with several old petrified tuberculous lesions, probably of primary character, without lymph node changes. The reinfection complex was typical in every respect, with a large, completely caseated parenchymal focus, 10 to 13 mm. in diameter, in the middle third of the left upper lobe near the lateral surface. Three regional lymph node groups, including the bronchopulmonary, upper tracheobronchial and paratracheal on the left side, were slightly enlarged and diffusely caseated; in some of them there was soft central disintegration with formation of minute cavities. On the X-ray film the reinfection complex cannot be recognized clearly; there is only a very faint density at the site of the focus and about the bronchopulmonary and paratracheal lymph nodes. There is no trace of a chalky or calcified deposit.

It remained for the complete histological analysis to prove that we actually were dealing with a much less complicated pathogenetic problem than the X-ray photograph would have led one to believe. Only one of the firmly calcified lesions—that in the base of the left lower lobe—was a typical obsolete calcified-ossified primary focus. All the other calcified structures, in the subapical portion of the left upper lobe, in right middle and right lower lobes, were anthracosilicotic nodules. The lymph nodes draining the area of the old primary focus were not examined histologically in this case; neither on the X-ray photograph nor at gross dissection was any tuberculous lesion seen. A microphotograph of the old primary lesion, of the reinfection focus and one of the regional caseated lymph nodes is shown on plate 6. The structure of the primary focus is in every respect typical for an old obsolete stony-ossified lesion. There is some bone marrow, containing anthracotic pigment, attached to a very firm hyaline capsule in part surrounding the calcified core. In this the ring-like bands are clearly seen. In the photograph of the soft reinfection focus there is some evidence of minute central disintegration. The encapsulation of the diffusely caseated areas is fairly firm. There are many typical Langhans' giant cells. The histological picture of the large, firmly caseated conglomerate tubercles in the regional lymph nodes, all of which were examined, is typical in every respect; they replace most of the lymphoid structure. In some of them there is distinct central disintegration. In these the material was soft, and irregular cavities were seen grossly.

There were, in addition, several soft fibrous-cheesy tubercles, mostly in subpleural portions of both lungs; also in spleen, liver, kidneys, and a rare tubercle in the myocardium, representing a scattered hematogenous seeding from the reinfection complex.

Case 7: (B. G. H. 5007) Forty-one year old colored female. Cause of death: miliary tuberculösis. (See plates 7a, 7b and 7c)

The primary complex consists of a single calcified, well encapsulated focus, between 2 and 4 mm. in diameter, in the midportion of the right upper lobe, and of two firmly calcified lymph nodes in the regional upper tracheobronchial group, one small bean sized, the other pinhead sized.

The left lower tracheobronchial lymph nodes were found completely caseated. Careful inspection of the left lung disclosed a well encapsulated, pea-sized caseated focus in the lower-most portion of the left upper lobe just in the angle between anterior and interlobar surface within the lingula, with a second, somewhat smaller, similar lesion very close to the former and also closely connected with the pleura. There was about one quart of partly organized fibrinous and hemorrhagic exudate covering the area about the lingula, extending toward the mediastinal pleura, and about most of the basal and lateral surface of the left lower lobe. A few lentil-sized tubercles were seen in the diaphragmatic pleura facing

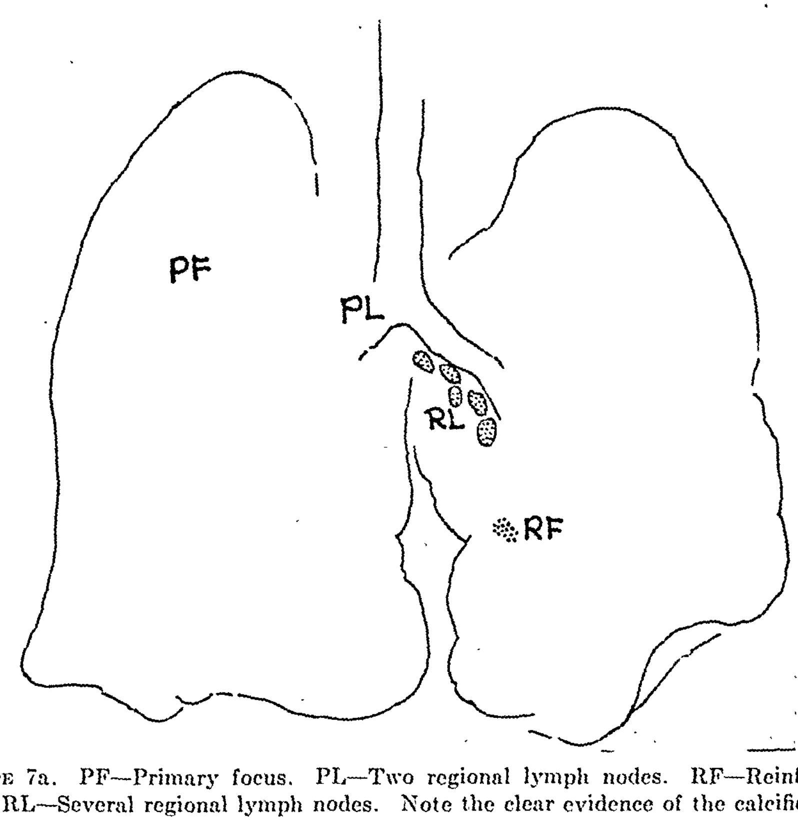


PLATE 7a. PF—Primary focus. PL—Two regional lymph nodes. RF—Reinfection focus. RL—Several regional lymph nodes. Note the clear evidence of the calcified primary complex in the X-ray photograph. The whitish speck to the left of the upper trachea represents a calcified adenoma of the thyroid. Note also the dense diffuse miliary tuberculosis and the atelectatic shadow in the left lower lung field.

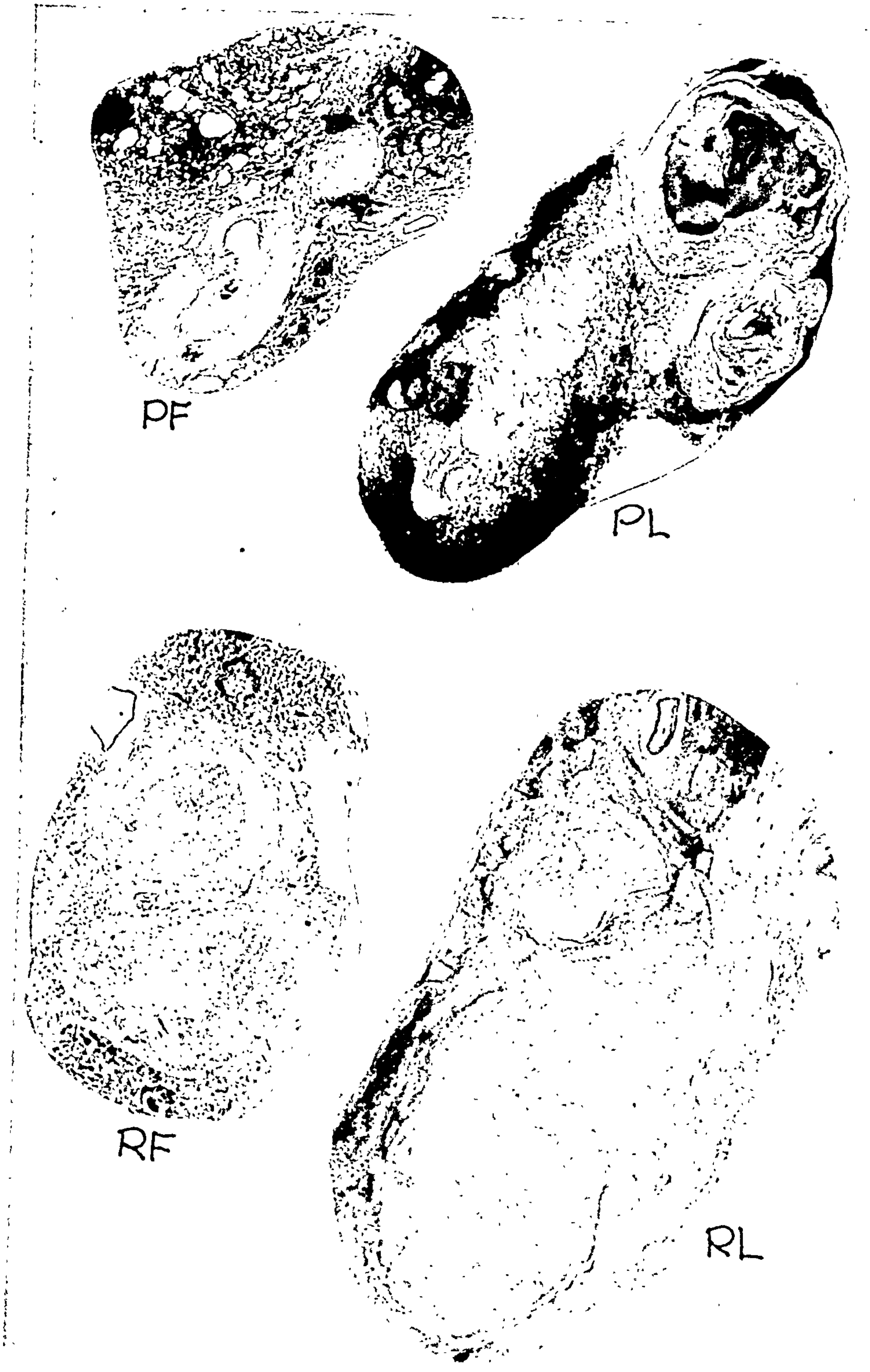


PLATE 7b. PF--Primary focus in firmly calcified state with a hyaline capsule. PL - One of the lymph nodes regional to the primary focus, with two firmly encapsulated calcified tubercles. RF - Reinfection focus consisting of two soft, caseated nodules, distinctly encapsulated. Note their subpleural position, especially that of the lower nodule. RL - Diffuse caseation in one of the lower tracheobronchial lymph nodes regional to the reinfection focus.

PLATE 7c. Upper—one of the typical pictures of recent miliary tubercles with central caseation, forming conglomerate tubercles. Lower—section through the tuberculous pleura and underlying atelectatic lung tissue. More detailed explanation in text.

the left lung. There were densely arranged miliary tubercles in both lungs. Some of these, especially in the area near the reinfection lesion, were slightly larger than in the remainder of the lung. The entire picture was otherwise that of a typical dense miliary seeding. There was no gross caseation in any lymph node group regional to both lungs, apart from the left lower tracheobronchial group. In a few lymph nodes, especially in the anterior mediastinum, distinct miliary tubercles could be seen with the naked eye, and the lymph nodes in both venous angles were slightly enlarged, suggesting recent tuberculous hyperplasia. There was extensive hematogenous tuberculosis of both kidneys—with the cortical tubercles involving the kidney capsules—of the peritoneal surfaces, liver and spleen. Both adrenal glands showed considerable caseation and the periaortic lymph nodes showed tuberculous hyperplasia. Death was caused by a typical tuberculous meningitis.

An epicritic analysis of all the gross findings revealed a reinfection complex in firm caseated state, with the pulmonary focus in close subpleural position and with extensive active tuberculous pleuritis restricted to the left lung, especially marked about its base. The complex of first infection, in the opposite lung, was firmly calcified and restricted to a small parenchymal lesion and two regional lymph nodes. The extensive tuberculous pleuritis about the left lower lobe seemed to point to the focus of reinfection as its source, as this was the only older caseated and by far the largest encapsulated lesion in the left lung. The miliary tuberculosis most probably was caused by the extensive tuberculous pleuritis. The intestinal tract was entirely free. Whether the peritoneal tuberculosis was strictly hematogenous or secondary to the tuberculous pleuritis could hardly be determined. There was no serous or fibrinous exudate in the peritoneal cavity.

The histological examination included: the primary complex in all its components, the entire lymph node chain between the right lung, the angulus lymph nodes and the remainder of the bronchomediastinal lymph nodes draining both lungs; various sections from all lobes and especially the entire area of the reinfection focus, the regional lymph nodes, various pleural tubercles from the lingula of the left upper lobe, and the interlobar surface and basal area of the left lower lobe with the distinctly thickened pleura. Plates 7a, b and c show the postmortem X-ray photograph, first and reinfection complex and representative sections of the tuberculous pleura and the pulmonary miliary tuberculosis.

The primary focus is firmly calcified and surrounded by a hyalinized capsule. There is a bud-like hyaline extension. The surrounding lung tissue shows moderate scarring, especially at one pole of the lesion, but nowhere is there any active granulation tissue. The regional lymph nodes contain two large calcified tubercles within firm hyaline walls. In the remaining lymphoid tissue of this node there are a few hyalinized conglomerate tubercles but also recent caseated miliary tubercles. This latter finding is obviously the effect of the overwhelming miliary tuberculosis. In all lymph nodes draining the right lung the histological analysis revealed small conglomerate tubercles with central caseation and occasionally small hyalinized conglomerate tubercles alternating with more recent epithelioid cell tubercles. In none of them, however, are there any chalky or calcified changes. The hyalinized tubercles gradually blending with epithelioid cell and caseated tubercles present a picture frequently seen in lymph nodes draining the site of massive tuberculous lesions in prolonged hematogenous seeding. These same findings were present also in the right lower tracheobronchial lymph nodes.

The lesions forming the reinfection complex are shown on plate 7b. The reinfection focus consists of two caseated nodules, situated near to each other, surrounded by a hyaline wall and atelectatic lung tissue. The pleura above the foci is thickened by chronic

tuberculous inflammatory granulations. The lymph nodes regional to this area show diffuse caseation along with a few small hyalinized conglomerate tubercles near the capsule. These were the only lymph nodes which showed diffuse caseation; in all others there were only miliary epithelioid cell tubercles and a few small hyaline conglomerate tubercles, as seen in the lymph nodes draining the right lung. Various sections taken from all lobes showed a picture more or less similar to that seen on plate 7c, with fairly recent miliary tubercles with central caseation, here and there forming larger tubercles by agglomeration. The distribution of miliary tubercles was the same throughout the right lung and in the upper and central portions of the left upper lobe. In the left lower lobe, however, which was distinctly atelectatic, the miliary tubercles were fewer in number and comparatively small in size. Several sections taken through the lingula of the left upper lobe, the interlobar surface and base of the left lower lobe—including the tuberculous pleura about the atelectatic lung tussue—showed very severe changes of specific tuberculous pleuritis with caseated tubercles and with many epithelioid cell tubercles in the parenchyma underneath. In some sections (see the lower picture on plate 7c) the large number of epithelioid cell tubercles within the visceral pleura was clearly noticeable; also the *atelectatic lung tissue, the hemorrhagic necrotic exudate covering the pleural tubercles,* and the capillarized granulations between these tubercles and the surface, which was obscured by a layer of fibrinous exudate.

The visceral and parietal peritoneum were studded with innumerable small tubercles, histologically of the typical epithelioid cell pattern. There was also recent tuberculosis of both tubes, involving the entire mucosa and part of the serosa, obviously of the descending type secondary to the peritoneal dissemination. Kidneys, liver and spleen showed uniformly recent miliary tubercles with diffuse caseation in many of them. In some conglomerate tubercles of the kidneys there was fibrous organization in their centre. All lymph nodes about the aorta, liver and pancreas, and several retromediastinal nodes in close topographic relation to the thoracic duct showed conglomerate tubercles with considerable caseation. This was seen also in a section taken through a small lymph node attached to the thoracic duct. It showed recent caseation involving the duct wall. There was extensive caseation in the adrenal glands, more marked in medullary portions than in the cortex, in which a few nodular regenerates had remained. There were no tuberculomata in the brain substance, but the typical gross picture of tuberculous meningitis.

Epicrisis: In addition to the components of the old and the reinfection complex and various areas of the tuberculous pleura of both lungs, with the entire bronchomediastinal lymph node chain of each side, all organs were examined histologically. The tuberculous lesions outside of the lungs were all of a comparatively recent state, as were the obviously hematogenous miliary pulmonary tubercles. The intestinal tract, apart from the miliary seeding into the peritoneal coat, was entirely negative. As the primary complex was in firm, fibrocalcified state, and the reinfection focus in the left lung the only large, firmly caseated lesion, it was the reinfection which apparently furnished the source for the overwhelming hematogenous tuberculosis. On the basis of the structural appearance of both components of the reinfection complex—lymph nodes and focus—associated with chronic tuberculous pleuritis about the lower part of the left lung, it seemed that this hematogenous dissemination was brought about

in connection with the extensive tuberculous pleuritis around the site of the reinfection focus.

This patient was admitted with a low grade septic type of temperature and signs of fluid in the left chest. There were no breath sound about the entire left chest. Fever persisted throughout the entire course of her disease. Repeated taps failed to demonstrate tubercle bacilli. Although miliary tuberculosis was suspected clinically, three tuberculin reactions were negative, and only two weeks previous to the fatal termination the X-ray film became suggestive of miliary tuberculosis. Typical symptoms of tuberculous meningitis were present only a few days before death. This patient, a housewife, had been in good health all the time until exactly three months prior to her death.

DISCUSSION

A review of the 29 cases with a reinfection complex listed in the table reveals the following data relative to age: 4 were in the third decade, 3 in the fourth, 3 in the fifth, 9 in the sixth, 5 in the seventh and an equal number in the eighth decade. In the 2 cases with active tuberculosis, clinically recognized, the ages were forty-one and fifty-seven. In all age groups the anatomical picture is entirely clear. This especially applies also to the 4 cases found in the third decade, between twenty-four and twenty-seven years of age. The structural distinctions were just as clear in spite of the fact that in reinfection focus and regional lymph nodes chalky changes could be already noticed within the firmly encapsulated caseated tubercles. In all of these the primary complex or the primary foci were in a completely obsolete state.

A comparison of the various histological structures with the X-ray pictures revealed that the radiographical appearance of a shadow-giving lesion might be misleading as to the true nature of such a calcified or chalky focus. We have found that especially soft, comparatively recent chalky lesions gave a very compact whitish shadow, suggestive of considerable calcification. In spite of this they could easily be cut through their center without any decalcifying procedure.

The structural age distinctions between the lesions of the first and reinfection are in most of our cases very clear. In some of them (4701, E-124, table 1), however, distinct calcification was also present in the components of the reinfection complex, although the bulk of the tuberculous changes appeared still in a diffuse soft chalky-fibrous state, occasionally with considerable lipoid debris. Focus and lymph nodes forming the primary complex were found in a uniformly petrified and ossified state, characteristic of old obsolete infections. That advanced structural ages in both complexes might approach each other more closely is indicated by case 4587, in which reinfection focus and regional lymph nodes were already in a fibrocalcified state. There was even localized marginal bone formation in the lesion designated as the reinfection focus. The primary focus was in a uniformly ossified, firm stony state; the regional lymph nodes in particular contained very firm stones within thin bony trabeculae. In the

lymph nodes of the reinfection complex, however, such stony matter had not formed as yet. It is rather surprising that not more cases were found in which these structural distinctions were less conspicuous. That regression follows the same pattern in the components of a reinfection complex, leading eventually to firm stone formation, was alluded to in our previous paper on complexes of different age. It is probable, however, that in later life regressive changes in tubercles take place at a slower pace than in childhood and early adult life. Such an opinion was voiced first by Schuermann in discussing the time required for calcification and stone formation in postprimary lesions in general, as compared to the components of the primary complex.

There seems to be no indication from our limited experience at hand that the findings of a reinfection complex are restricted to the white race. There are 2 colored cases included among our total of 29. One of them terminated in miliary tuberculosis with tuberculous meningitis.

Number, location and size of the primary and reinfection foci are given in the third and fifth columns of the table. As to the primary foci, they were single in 21 cases, in 5 there were two, and in one case there were four foci of identical structure. In 2 cases the primary parenchymatous focus was not found, although in one of these a minute speck in the X-ray photograph was suggestive of a calcified structure. The reinfection focus was single in 27 cases, and only in the remaining 2 were there two or more reinfection foci. In one of these latter there were two foci in the same lobe, in the other there were several small focal lesions in the left upper and a considerably larger one in the opposite lung; two reinfection complexes had formed, one in each lobe.

Comparing the location of primary and reinfection foci, the following is learned from the table: In 18 cases they were in different lungs, in 3 cases in the same lung, and in 4 cases in the same lobe. Also, in one of them, included in this latter group, there was an additional reinfection complex in the opposite lung. The remaining 4 cases showed various combinations. There were several older foci or two old complexes in different lungs.

A comparison of the size of primary and reinfection focus reveals the following figures: The old primary foci ranged between 1 and 3 mm. in 19 cases; 3 to 5 mm. in 8 cases; and 7 to 10 mm. in one case. The size of the reinfection foci is considerably larger. The following size ranges were measured: between 1 and 3 mm., 2; 4 and 5 mm., 4; 5 and 18 mm., 20; 21 and 25 mm., 3. From the gross and X-ray appearance of some of these unusually large reinfection foci with their diameters between 18 and 25 mm., usually of round or ovoid shape, it is probable that they might be discovered incidentally in roentgenological chest examinations. Some of the "tuberculomata" diagnosed radiographically might, therefore, represent single reinfection foci. Long (4) has mentioned one interesting clinical observation in a patient in which a reinfection complex, called by Long a "second" primary infection, could be demonstrated roentgenologically. This patient had first shown X-ray evidence of calcified lesions. His previously positive tuberculin reaction became, in the course of further ob-

servation, negative. With the radiological appearance of a reinfection "of the primary type," the tuberculin reaction became positive again.

As was to be expected, there is no noteworthy difference in the location of primary and reinfection foci in regard to the different lobes. In the left upper there were thirteen primary foci and ten reinfection foci. The corresponding figures for the left lower lobe are four and eight, for the right upper twelve and five, for the right middle three and six, and for the right lower three and two. The upper-most portion, the so-called apex, of both upper lobes was in no case the site of either the primary or the reinfection focus. If we consider the locations in their projection to the upper, middle and lower field in each lung, our figures quoted above read somewhat differently. In the left upper field there were five old foci and four reinfection foci. The comparative figures for the right upper field are six and three, left middle field eight and four, right middle field twelve and eight, left lower field four and ten, and for the right lower field 0 and two. In this limited group it appears that there were more reinfection foci in the middle and lower fields than in the upper fields. The location of primary focus and reinfection focus was found at fairly symmetrical levels of both lungs in 12 cases.

In regard to the lymph node changes within the primary and reinfection complex, it should be stated first that in 7 instances there were no regional lymph node changes to the primary focus or foci. The reinfection complex in these cases included one lymph node group in 2, two lymph node groups in 3, and three lymph node groups in the other 2 of these 7 cases. In the remaining 22 cases the extent of the tuberculous changes in the lymph nodes regional to the primary and reinfection focus or foci was about the same in 14 cases. In 7 it was greater in the reinfection complex, and only in one the lymph node changes were more extensive in the primary complex.

As to additional old lesions apparently in connection with the primary complex, there were positive findings in 2 cases only, in one of them a calcified-ossified tubercle in the opposite lung (case 5123). In this case the primary focus was not found, but lymph node changes and also a minute speck on the X-ray pointed to the right middle field as the area of the primary complex. In the other case there was localized focal extension to the apex of the same lobe in which the primary focus was found. The primary lesion was in the subapical field of this lobe. Apart from these two findings, there was no evidence of old calcified or stony tubercles, either in the lungs or in other parenchymatous organs as far as this could be decided by careful gross dissection.

Additional findings in connection with the reinfection complex were more prominent. All these, including focal extension and clearly hematogenous tubercles in the lungs and in extrapulmonary organs, are listed in the last column of the table. There was recent perifocal spread within small bronchi around the reinfection focus in one case; to the apical area of the same lobe—the reinfection focus being in subapical position—also in one case; within both lobes of the same lung, from two reinfection foci in the left lower lobe also in one case; to

the opposite lung only in 2; and to both lungs in one. This focal extension was in general restricted, leading to small bronchial and peribronchial tubercles of the same fibrocaseated or caseated-chalky structure as found in the reinfection focus. A few of these additional lesions were of very small size and therefore appeared in a more advanced fibrous organization than the reinfection focus.

In 2 cases of our series there was tuberculous pleuritis around the reinfection focus; in both the focus was in basal location. In one of them the pleuritic exudate was already in an advanced state of organization. This was an entirely incidental finding which was not recognized clinically (case 4689). In the other, although the pleuritic exudate was in part already organized, there were many caseated pleural tubercles about the reinfection focus and the adjoining basal areas with hemorrhagic exudate, associated with generalized miliary tuberculosis. Anatomical and histological analysis pointed to the reinfection focus as the source of this tuberculous pleuritis.

Apart from the last 2 cases with active tuberculosis recognized during life, scattered miliary hematogenous tubercles were found incidentally in 9 cases of this series. The histological structure of all of these pointed clearly to the reinfection complex as the source. They were in the liver and spleen in 5 cases, in recent caseated fibrous-cheesy or —in one instance—in chalky-fibrous state; in liver, spleen and both lungs in 2 cases; and in both lungs, liver, spleen, and kidneys, and myocardium, respectively, in 2 cases. In all of these last 4 cases the tubercles showed a relatively recent caseated or fibrocaseated structure. These findings of scattered hematogenous tubercles, especially in the liver, spleen, kidneys and in the lungs, are in line with our previous experience in a few cases of late primary tuberculous infections, as reported in one of our previous papers (VI).

We have listed in the last column of our table, among additional findings, also such structures which by their radiographical appearance can be mistaken for calcified tubercles. As we have stated, in one of these cases (no. 5123) such foci might give an entirely false topographic impression of the components of the primary complex, or might appear as additional foci of primary character, without direct relation to the complex. Only after the true nature of all these calcified structures was disclosed by histological examination, was the identity of the primary focus or foci in their relation to the primary complex really unmasked. The size of most of these calcified or ossified lesions was not smaller than that of the true obsolete primary foci. It is essential for an accurate analysis of pathogenetic problems posed by tuberculous lesions in the lungs that all such calcified stony or osseous lesions, as found at dissection and especially on the postmortem X-ray film, should be examined without exception. There were, in 8 cases, calcified anthracosilicotic structures within small intrapulmonary lymph nodules. They were found in the upper and hilar levels of both upper lobes, including the area near the apex, but also in the right middle lobe and in the right lower lobe. Calcified anthracosilicotic structures in bronchopulmonary and tracheobronchial lymph nodes were present in 3 cases, "*osteomata*" in 7, and phleboliths in 2. It has been found in our experience, in several hundred

cases systematically studied, that these small "osteomata" can occur also as single structures and not necessarily in multiple fashion as stated in the literature. More will be said as to the relative frequency of these intraälveolar osseous structures and their relation to certain diseases in one of our forthcoming papers dealing with calcified and ossified structures of nontuberculous origin.

In the epicritic discussion of the individual cases presented in our previous papers on the reinfection complex (1) it was pointed out why the morphologic analysis permitted of no other conclusion than to consider the additional Ranke complex as the result of a true reinfection. It was the anatomically healed (obsolete) state of the primary complex or—in some cases—of the primary lesion restricted to the pulmonary parenchyma, the absence of any other older lesion which might have formed an endogenous link, and especially the anatomical picture of the second, structurally less old or comparatively recent, tuberculous complex which pointed to but one pathogenetic mechanism: a true exogenous reinfection simulating the classical primary complex (Ranke). In the cases previously reported as well as in the new series presented in this paper, the distinction in the structural age between the components of the primary complex and of the reinfection complex suggested strongly that the latter was acquired at a much later time than the former. In fact, the conclusion seemed to be permissible that the old primary complex was apparently in a completely healed or in a progressively healing state when the reinfection occurred. The obsolete petrified or firmly hyalinized encapsulated remnants of the first infection had remained, but these and whatever additional lesions had formed in connection with the primary infection were total scars, devoid of specific granulation tissue. That additional exogenous infections might lead to the establishment of a new reinfection complex, at a time when the firmly petrified or ossified state is not as yet reached, was seen in very few instances in our material. One of these was reported in paper XI (1), in the first case (pages 156–161). It was a combination of an old obsolete calcified-ossified focus, a reinfection complex in diffuse chalky state in firm encapsulation, and a more recent, additional complex with a locally progressing cheesy focus and recent caseated tubercles in the regional lymph nodes. This latter complex was interpreted as the result of a superinfection In one of our cases included in this series, the only one with overwhelming miliary tuberculosis, primary focus and regional lymph nodes had not as yet reached the firm stony or ossified state, although they were calcified and firmly encapsulated by hyaline tissue.

The criteria, then, used in correlating the structural ages of the various lesions of the primary with those of the reinfection complexes are strictly relative or comparative. They have been used for a long time by pathologists interested primarily in the pathogenetic analysis of tuberculous lesions. It has been an elementary concept of tuberculosis pathology that a soft caseated focus is younger than a firm fibrocaseated, chalky or calcified one; that it gradually changes through various phases, including chalky regressions, partial or complete fibrous organization, more or less firm calcification, stone formation and ossification. The reader is referred to our general discussion of the criteria of structural age

difference in one of our previous papers on recent primary tuberculosis in adults (VI, pages 88–90), and to our discussion of Bloch's paper on radiographic-pathological correlation of tuberculous calcifications in the lung (5).

We have presented our anatomical findings on the reinfection complexes in all necessary detail. Inasmuch as in most of these cases they were not complicated by chronic tuberculosis of the lungs or other organs, a complete pathogenetic and morphologic analysis could be carried out. Such findings of reinfection complexes in the lungs, documented by detailed roentgenological, anatomical and histological study of all lesions present, were formerly not known.

It was only by careful anatomical observation and dissection that our knowledge of the primary complex was obtained. As Schuermann stated, the work of Kuess and Ghon on the primary complex became of such importance only because their findings were presented in complete detail which, in contradistinction to the reports of others (to mention especially E. Albrecht, Foedisch, H. Albrecht, Hedrén) could be checked in every respect. Only in Ghon's and Kuess' work were all characteristic features of the anatomical changes—which later became known as the primary complex—strictly observed. Regardless of what we eventually might learn of the clinical significance of the reinfection complex in its relation to the pathogenesis of tuberculosis in general—so far the number of cases with progressive pulmonary tuberculosis in connection with the reinfection complex was comparatively small—exact morphologic research is just as essential in this field as it was in the classical analysis of the primary tuberculous infection in children by Kuess and Ghon. It should include each and every single lesion of the first and reinfection complex.

From the data given in case 128 in the book of Sweany entitled *Age Morphology of Primary Tubercles* (6), it is obvious that the anatomical picture was greatly complicated by large cavities in both upper and the left lower lobe. Whether or not this chronic progressive pulmonary tuberculosis in a female, twenty-six years of age, was initiated by a true reinfection complex cannot be stated with any degree of certainty from the anatomical and histological findings given. Of five calcified lesions, only three were examined histologically. Nothing is said about the relation of these calcified tubercles to the cavities and the probable structural age of the latter. In addition, of the calcified lesion in the left upper lobe, which was the largest of all (4 mm.), and of the regional hilar node, no histological data are given at all. Sweany's interpretation is that two calcified lesions, one (3 mm.) in the right lower, the other (2 mm.) "near the hilum" (whether in a lymph node or in the lung tissue is not stated), declared a "7-year type," represent a repetition of a primary complex which had occurred years after a tiny (2 mm.) and much earlier primary lesion in the left base, declared as an "18-year type." (This latter reference is not entirely clear; it most probably should read "the" small lesion in the left base instead of "one" small lesion.) As Sweany has stated (p. 77) that the process of bone formation may advance faster in tubercles 2 to 3 mm. in diameter than in larger lesions, there is even less reliance on the correctness of specific age estimates, if applied—as in this case—to calcified tubercles below the size declared best suitable for his "age formula."

I have cited this case not only in order to contrast its analysis, obviously incomplete, with the material on proved reinfection complexes, but also for the following reason: In discussing the structural age difference of the three histologically examined calcified lesions Sweany, in referring to a "repetition of a primary complex," states that "this phenomenon has been described by Terplan, and I have observed it occasionally, although it is difficult to find adequate evidence to prove it." In the review of Sweany's book (7) I mentioned the case quoted above not because I did consider it as a clear example of a reinfection complex—extensive cavities considerably complicated the picture—but to call attention to Sweany's reference to the reinfection complex which I had described, stating "... curiously, exactly for this phenomenon [meaning a complex of reinfection] for which *the different structural age is the deciding issue*, he [Sweany] claims it difficult to find adequate evidence for proof." His book was published in 1941.

In the September, 1942 issue of the American Review, however, in a paper entitled *Age Characteristics of Tubercles* (8), Sweany presents a very different view. Now he declares, "Not infrequently, perhaps even commonly, there are reinfections simulating the primary complex." Then he refers to Schuermann's and especially my own description of the reinfection complex, and continues, "No doubt many of these are virtually primary lesions because the true primary was so slight that it caused little basic change in the host. The only reason they are not accepted readily is because of the difficulty in proving their true nature." Then he advocates the application of the "age-morphology pattern, ... as this will help to recognize more of these infections."

To this it should be stated that our knowledge of the intestinal reinfection complex is based almost entirely on 11 cases of Schuermann. As to the pulmonary reinfection complex, there are, apart from our own findings (1), no other adequately examined anatomical reports. I do not know, therefore, on what authority—aside from these reports—Sweany's statement as to the possibly common frequency of the reinfection complex is based. It could not be derived from his own material as far as this has been published. What the relative frequency of the reinfection complex is we cannot state at the present time. The material analyzed by myself is not large enough in this respect, but relative to the pulmonary reinfection complex, ours are the only figures available (apart, perhaps, from 4 instances briefly mentioned by Hesse, to which I referred in one of our previous papers (1)). War conditions did not permit examining systematically our entire postmortem material in the past five years. Any attempt, therefore, to relate the number of cases in which reinfection complexes have been demonstrated to the number of postmortem examinations performed during the same period could easily give an erroneous impression. It is intended, however, to discuss this problem in its proportion to reinfection in general in a special paper dealing exclusively with the pathogenesis of active tuberculosis as found in our material.

What we first need, then, is careful anatomical dissection and analysis of a larger material because so far the anatomical findings are the only absolute proof of the reinfection complex. It is frequently not in agreement with our

findings to assume that the primary infection was "slight" whenever a reinfection complex has developed in the same case. In an anatomical sense, the remnants of the primary infection in these cases are not different from many other closed primary complexes as seen in general routine postmortem examinations. In one of our observations, previously reported (IX) (1), the primary pulmonary complex had caused diffuse tuberculous peritonitis and ophoritis. The deciding issue is that the primary infection—in these cases—had apparently completely healed and that its bearer was exposed to a reinfection.

In most—if not all—of our cases which we have presented in previous papers, the anatomical findings were clear and the difference in the structural age of the lesions in question was very distinct. This, alone, enabled us to present them as reinfection complexes. Their nature, we believe, has been proved beyond any doubt and their analysis was comparatively simple, as can be learned from the individual case reports. I do not know, therefore, in whose name Sweany speaks when he stated that "they are not accepted readily." Whatever is generally known to the student of tuberculosis pathology of the relative differences in the structural age of tubercles is entirely sufficient in the pathogenetic analysis of reinfections, presenting the picture of a Ranke complex. This comparative analysis alone has been used throughout our pathogenetic studies of the various types and combinations of primary and postprimary tuberculous lesions. The heading selected for our first paper (1), "Complexes of Different Age," indicates that the relative age estimates used by this strictly comparative approach were thought sufficiently reliable. My attitude to the arithmetical type of computing the ages of primary tubercles, as introduced by Sweany, has been clearly stated in the review of his book. With regard to the topic of our discussion—the reinfection complex—we feel that the anatomical facts presented in this field appear satisfactorily documented and that there is no need for a specific "age formula" to make such pathogenetic studies more successful.

APPENDIX

To Sweany's repeated claim (8) that "the conception of the age-morphology relationship is essentially new," I shall cite only a few facts not in agreement with this claim—presented in such a general form—from an admirably thorough historical account of the gradual evolution of our knowledge of primary tuberculosis, as given by Schuermann (3). Ribbert referred to encapsulated calcified foci in the lynph nodes of children and adults as the oldest lesions and called them, therefore, primary. Also, to Lubarsch and Pollack the stony structures in various lymph nodes and in the lungs indicated a relatively old age, and ossification, in particular, was looked upon as probably the oldest of the regressive metamorphoses of the caseated tissue. Kuess, too, stressed the relative oldest structure in various of his cases. Ranke pointed to the calcification and eventual complete petrifaction of the caseated tissue as something very regular. The stony remnants of the primary complex might persist for years or decades without being conspicuously changed. In Ghon's work the criterion of the "oldest age" was used in his pathogenetic studies, together with the anatomical picture of the primary complex. In a paper published together with Pototschnig, he frequently discusses the limitations of the age determination on the basis of structure alone. As to primary infections in early adult life, Ghon pointed out that the quicker and more completely they heal the more difficult it must become to differentiate them from the obsolete scars of

any primary childhood infection. That the components of a primary complex might not necessarily heal at the same pace was pointed out by Huebschmann. The lymph nodes might still persist in a less obsolete state while the primary focus is already firmly calcified or even ossified.

Schuermann, in analyzing his own material of 1,000 cases, found that the tendency to caseation and comparatively rapid calcification helped to utilize one, "in general not very safe," criterion of relative age. The use of this criterion, together with the observance of the topographic relation of the components of the primary complex, was instrumental in determining the portal of entry in 95 per cent of all cases from all age groups. Schuermann, in addition, deals, in a special paragraph (of 25 pages), exclusively with the age of the foci forming the primary complex. In the table in which the various stages of these lesions are presented the sequence pointing to the gradual aging is as follows: noncaseated, caseated, older caseation, caseated-chalky and petrified—this latter term including firm calcification and ossification. At various occasions Schuermann mentions the age factor in comparing focus and lymph nodes forming the primary complex. From some individual case reports presented in his material, it is also clear that bone formation was looked upon as a state which was preceded by firm calcification. It is in this paragraph that Schuermann, for the first time, calls attention to the intestinal reinfection complex. Yet, it is said of Schuermann that "though he actually showed that the presence of bone [in focus or lymph nodes of the primary complex] increases in the older age groups" he did not attempt to "establish any relationship of age to morphology."

In the same connection, Sweany, in regard to "the age-morphology relationship" refers to Grethmann, who, he claims, dogmatically denied any such relationship. The paper of Grethmann (9), quoted as basis for this claim, deals exclusively with the pathology of acute disseminated miliary tuberculosis, but not at all with the primary tubercle. In this study, presenting a very thorough histiogenetic analysis of the acute interstitial miliary tubercle in lung tissue, Grethmann points to the difficulties of determining exactly the age of tubercles in a disease of relatively short duration. If such a morphologic criterion of age, as a distinctly established capsule, readily staining with van Gieson, with more or less pronounced hyalinization, was correlated with the known clinical data, it was found that these fibrous capsules could be demonstrated already in cases in which the duration of the clinical disease was very short. In agreement with Weigert, Arnold, Benda, Tendeloo, Hartwich and Korteweg, Grethmann stated that morphologic criteria, even in a disease of such a limited duration as acute disseminated miliary tuberculosis, are rather crude, and the age of this disease cannot be exactly determined. Mistakes by several weeks might be made in a disease lasting from between two and eight, or two and eleven weeks, if both types of acute disseminated hematogenous miliary tuberculosis—the exudative miliary and the productive miliary—are included.

My own attitude to this "age-morphology conception" is not different from that of Ghon and Schuermann. It is inconsistent to claim that I "apparently" deny *any* relationship between structural changes and the age of a lesion, and then to quote, only a few pages farther on in the same article, my contributions to the reinfection complex, for the clear establishment of which differences in the structural age are the deciding issue. "Essentially new" is, as stated in the review, only the attempt to *absolute* age estimates of a primary tubercle in the various phases of regression, especially in terms of specific numbers of years applied to each of those stages. The author's admission that his age formula is perhaps too complicated for common use is difficult to be reconciled with advocating its general adoption.

Sweany calls it a "grave misapprehension and a careless quotation" when I stated that his monograph was based on postmortem material exceeding 900 lung specimens. In presenting his plan of study, he explains in detail how the postmortem roentgenograms were taken, how the calcified lesions were studied, located, recorded, sectioned, etc. Then he states literally (page 17), "after working up over 900 specimens by this method," etc. I neither assumed nor stated that all 900 cases were tabulated. They certainly were "worked up" by the method described in the plan of study, from which I quoted. My criticism, how-

ever, that progress in our knowledge of tuberculosis is better served by more thorough analysis of a smaller material naturally includes the material listed in the tables. In a morphologic work of the type presented by Sweany, any number given as an "average figure" of lesions which were examined has no meaning, nor can one agree on which calcifications are "important." Each case is a problem in itself, because extent and number of lesions, including the calcified tubercles, vary widely. But all of these are important and have to be examined in a study of this nature if we want to expect unequivocal data, regardless how much one might disagree on their interpretation.

Sweany also objects to these errors: I quoted 11 mm. instead of 12 mm., and 30 cases instead of 27. It is obvious from the recheck of the original copy of my manuscript that these are printing (not typographical) errors which I could not correct as I had no opportunity to proof-read the review. In my copy it is 12 instead of 11 mm., and "about 30" instead of 27 cases. These errors are regrettable, though quite insignificant.

SUMMARY

The detailed anatomical findings in 29 additional cases of pulmonary reinfection complex are presented. In all, obsolete remnants of the primary pulmonary infection could be demonstrated, consisting in 22 cases of typical stony-ossified scars of the primary complex, while in 7 they were restricted to a single parenchymal focus. In only 2 instances tuberculosis disease had developed in connection with the reinfection complex, with tuberculous pleuritis, miliary tuberculosis and tuberculous meningitis in one, and with selective hematogenous tuberculosis of the tongue and adrenals in the other. Age, sex, race; size, location and structure of the primary and reinfection foci; extent and structural state of the corresponding lymph node changes regional to both primary and reinfection foci; additional tuberculous changes caused by either the old primary or the more recent reinfection; and all calcified or ossified lesions of nontuberculous origin in the lungs and bronchomediastinal lymph nodes are tabulated. Seven illustrative cases, including one with progressive hematogenous tuberculosis, are described.

Complete histological analysis of all calcified lesions is mandatory, as silicotic nodules in the intrapulmonary and bronchomediastinal lymphoid tissue, intra-alveolar "osteomata" and phleboliths might give—without histological control—an entirely erroneous impression regarding nature and topography of the components of the obsolete primary complex or of additional old postprimary tubercles. There is no noteworthy difference in the location of primary and reinfection foci in regard to the single lobes of both lungs; in their projection to the pulmonary fields, however, the middle and lower fields appear as a preferred site for the reinfection foci. The difference between the sizes of primary and reinfection foci is distinct. With one exception, the old primary foci did not exceed 5 mm. in diameter. The great majority of the reinfection foci measured between 5 and 18 mm., and a few, 21 to 25 mm. Such large reinfection foci might represent the substrate of "tuberculomata" incidentally discovered by X-ray examination. Extent of lymph node changes regional to primary and reinfection foci was about the same in 14 cases; in 7 it was greater in the reinfection complex; in one it was greater in the old primary complex. Lesions of focal extension and scattered hematogenous dissemination, incidentally found, were much more prominent in connection with the reinfection.

Although the pulmonary reinfection complex should not be considered as an occurrence of great rarity, careful anatomical investigation of a considerably larger material is needed in order to gain more accurate information as to its relative frequency and clinical significance. In the analysis of the structural age distinctions between the components of the primary and the reinfection complex, the strictly comparative method of relative age determination was used, as in the previous pathogenetic studies of tuberculous lesions in children and adults. In the quotation of the scarce data from the literature, attention is called again to Schuermann's anatomical reports of the intestinal reinfection complex.

SUMARIO

Preséntanse los hallazgos anatómicos pormenorizados en 29 nuevos casos del complejo de reinfección pulmonar. En todos pudieron observarse focos anteriores de la primitiva infección pulmonar, consistiendo en 22 de ellos en típicas cicatrices petro-osificadas del complejo primario mientras que en 7 estaban limitados a un solo foco parenquimatoso. Sólo en 2 casos se desarrolló enfermedad tuberculosa en relación con el complejo de reinfección: en uno con pleuritis tuberculosa, granulia y meningitis tuberculosa, y en el otro con tuberculosis hematógena selectiva de la lengua y suprarrenales. Hay tablas correspondientes a: edad, sexo, raza; tamaño, localización y estructura de los focos primarios y de reinfección; extensión y estado histológico de las alteraciones ganglionares correspondientes a los focos tanto primarios como de reinfección; nuevas aleraciones tuberculosas producidas por la antigua infección primaria o más reciente reinfección; y a todas las lesiones calcificadas u osificadas de origen no tuberculoso en los pulmones y los ganglios linfáticos broncomediastínicos. Descríbense 7 casos típicos, comprendiendo uno de tuberculosis hematógena evolutiva.

El completo análisis histológico de todas las lesiones calcificadas es obligatorio, pues los nódulos silicóticos del tejido linfoideo intrapulmonar y broncomediastínico, los "osteomas" intraalveolares y los flebolitos podrían crear—sin comprobación histológica—una impresión absolutamente errónea acerca de la naturaleza y topografía de los componentes del viejo complejo primario o de nuevos tubérculos post-primarios antiguos. No hay mayor diferencia en la localización de los focos primarios y de reinfección en cuanto a los distintos lóbulos de ambos pulmones; pero en su prolongación a los campos pulmonares, los medianos e inferiores parecen ser preferidos por los focos de reinfección. La diferencia en el tamaño de los focos primarios y de reinfección es bien definida. Con una excepción los antiguos focos primarios no excedieron de 5 mm. de diámetro, mientras que la inmensa mayoría de los de reinfección medían de 5 a 18 mm. y algunos de 21 a 25 mm. Esos grandes focos de reinfección pueden representar el subestrato de los "tuberculomas" descubiertos fortuitamente por el examen roentgenológico. En 14 casos, fué aproximadamente idéntica la extensión de las alteraciones ganglionares correspondientes a los focos primarios y a los de reinfección, en 7 mayor en el complejo de reinfección, y en uno en el

viejo complejo primario. Las lesiones de extensión focal y diseminación hematógena esparcidas, descubiertas fortuitamente, eran mucho más sobresalientes en los casos de reinfección.

Aunque no debe considerarse como muy raro el complejo de reinfección pulmonar se necesita una cuidadosa investigación anatómica de una serie mucho mayor a fin de obtener datos más exactos acerca de su relativa frecuencia e importancia clínica. En el análisis de las diferencias histológicas por edad entre los componentes del grupo primario y del complejo de reinfección, se utilizó el método estrictamente comparativo de determinación relativa por edad como se hizo en los previos estudios patogenéticos de lesiones tuberculosas en niños y adultos. En las citas de los escasos datos de la literatura llámase la atención nuevamente sobre los informes anatómicos de Schuermann acerca del complejo de reinfección intestinal.

REFERENCES

(1) Terplan, K.: Supplement to Am. Rev. Tuberc., vol. *42*, August, 1940: VII—Pulmonary complexes of different age, p. 99.
XI—Recent tuberculous complex in adults in the presence of an old calcified Ghon focus without corresponding lymph node changes, p. 154.
X—Older tuberculous complexes of different age, p. 140.
IX—Intestinal complex of recent exogenous reinfection, p. 131.
VIII—Progressive tuberculosis with tuberculous complex of true reinfection, p. 121.
(2) Schuermann, P.: Beitr. z. path. Anat., 1928–29, *81*, 568.
(3) Schuermann, P.: Virchow's Arch., 1926, *260*, 664.
(4) Long, E. R.: Am. Rev. Tuberc., 1939, *40*, 607.
(5) Bloch, R. G.: Tr. Nat. Tuberc. A., 38th annual meeting, 1942, p. 68.
(6) Sweany, H. C.: Age Morphology of Primary Tubercles, 1941, Charles C Thomas.
(7) Terplan, K.: Am. Rev. Tuberc., 1941, *44*, 490.
(8) Sweany, H. C.: Am. Rev. Tuberc., 1942, *46*, 329.
(9) Grethmann, W.: Beitr. z. Klin. d. Tuberk., 1928, *71*, 1.

TREATMENT OF EXPERIMENTAL OCULAR TUBERCULOSIS WITH PROMIN[1]

W. STEENKEN, JR., E. WOLINSKY AND F. H. HEISE

Experimenters are searching for better and more rapid methods of evaluating chemotherapeutic agents in animals. The following experiments were performed to learn whether ocular tuberculosis, which develops in a location that can be kept under constant observation, might provide a suitable site for such tests. Vaccinated animals were used as subjects because previous experiments (1, 2) had indicated that normal guinea pigs were so susceptible to the tubercle bacillus that the effects of therapy were not always clear-cut. This procedure seems justified in view of the fact that chemotherapy would probably be used in many human subjects that have already had one or more infections before the one resulting in clinical disease. In using this type of tuberculous lesion it was hoped that the influence of the drug might be apparent early and that the gross appearance of the lesions would indicate promptly whether further experiments were desirable. Promin,[2] whose value in the treatment of experimental tuberculosis in guinea pigs has been well established (1,3,4,5,6,7,8,9), was used to test the efficacy of the method.

METHODS

Sensitization: Forty-four adult guinea pigs were vaccinated with living attenuated human tubercle bacilli, strain H37 Ra, by injecting a suspension of 2.5 mg. of the bacilli subcutaneously in the right inguinal region on three alternate days, so that each animal received a total of 7.5 mg. of the microörganisms. Two weeks after the last vaccinating dose, all animals reacted with positive skins when tested with 5 per cent O.T.

Infection: One week after the skin tests had been recorded, all 44 vaccinated animals and an additional 5 nonvaccinated animals were inoculated in the anterior chamber of the right eye with a suspension of a fourteen-day growth of H37 Rv microörganisms from Proskauer and Beck's synthetic fluid medium. The suspension was so prepared that a microdroplet, when transferred to a slide and fixed, contained about 3 tubercle bacilli when examined by fluorescent technique (10). With a tuberculin syringe fitted with a B.D. No. 27 needle, one drop of this suspension, containing about 50 bacilli, was injected into the anterior chamber of one eye of each animal.

Treatment: The 44 vaccinated and the 5 nonvaccinated infected animals were divided into four groups: 18 to receive no treatment; 18 to be treated orally; 8 to be treated orally and locally, and 5 as nonvaccinated nontreated controls. The treatment with promin was begun the day following infection and was

[1] From the Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.

[2] Promin used in this study was kindly supplied through the courtesy of Dr. E. A. Sharp, Parke, Davis & Company, Detroit, Michigan.

continued daily for 295 days, when the experiment was terminated. The treated animals were all fed 75 mg. of promin in aqueous solution by syringe twice daily for fourteen days when the dose was increased to 150 mg. twice daily. The 9 treated animals that received the drug locally received their local treatment by dropping an aqueous 35 per cent solution of promin into the conjunctival sac of the diseased eye three times a day. The animal was held on its side so that the solution remained in contact with the eye for five minutes at each treatment. Previous experimental determinations of the promin levels in treated eyes showed us that this method was superior to using promin powder or ointment and that clamping the lid together after the instillation of the drug did not result in producing any higher levels of the drug in the eye. However, by the method used, levels of 2.0 to 5.0 mg. per cent were obtained by local treatment alone. It was also observed that after oral treatment alone the promin levels in the eye were about one-third those in the blood. Drug levels in the eye were determined by micromethod on tissue juice obtained from the entire eye.

Each eye was examined by at least two observers and the severity of the lesion was rated from 1 to 5. Rating 1 indicated eyes which showed only minimal lesions, usually consisting of a pin point area of corneal opacity and irregularity of the iris. A rating of 3 was given those eyes which showed definite redness with slight evidence of caseation in the anterior segment, moderate corneal opacity and cloudiness of the aqueous, and congestion of the iris. Rating 5 was reserved for eyes with advanced caseation, necrosis and perforation. Intermediate ratings were assigned accordingly. The index of ocular reaction was obtained by adding the total ratings for one group and dividing by the number of animals in the group. These ratings were made from week to week with no knowledge of what rating had been given the previous week. The animals were chosen at random from the various groups and presented to the observers, who had no knowledge of the group to which the guinea pig belonged.

The day after inoculation all the sensitized animals showed a marked allergic reaction, consisting of redness, edema and opacity of the inoculated eyes. The 5 unvaccinated pigs had only a slight traumatic reaction which cleared entirely within a few days. The progress of the ocular lesions is shown graphically in chart 1.

In group A (nonvaccinated controls) the eyes showed very little reaction until the second week, but from then on the lesions progressed rapidly so that by the fourth week the corneas of all 5 animals had perforated and caseation was advanced. From this point on the condition progressed till death.

The animals in group B (vaccinated controls) showed a marked allergic reaction, characterized by definite redness and opacity, which persisted for a few days after inoculation, but after a week it somewhat decreased. Then a localized tubercle developed which progressed slightly until the fourth week but thereafter remained more or less stationary. These lesions were much less severe than those of the unvaccinated animals and in none of the 20 did advanced caseation or perforation occur.

The animals in group C (vaccinated and treated orally with promin) and

group D (vaccinated and treated orally and locally) fared best. After the initial allergic reaction, the eyes appeared to improve until the second week, after which time tubercles appeared, but they progressed very slightly and always to a lesser degree than those in the vaccinated and unvaccinated control groups.

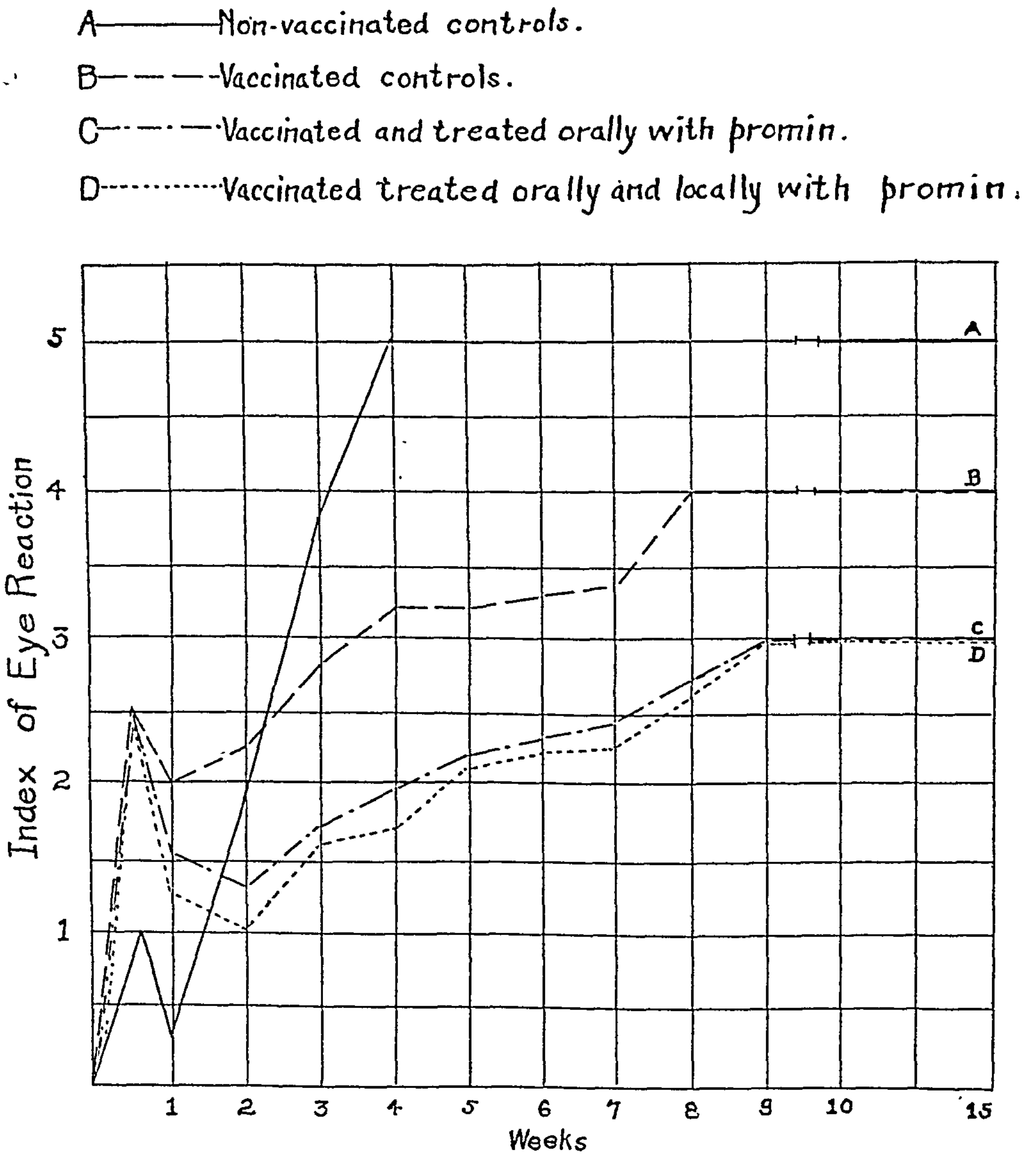


CHART 1

In the early stages of the disease, during the first three weeks after inoculation, the difference between the treated and untreated groups was most marked. In this period, too, the animals treated locally as well as orally seemed to be benefited more than those treated by mouth alone. This difference gradually diminished, and by the sixth week these two groups were essentially the same.

Throughout the experiment the differences between the untreated and the treated eyes were generally obvious. The former usually showed more corneal injection, iritis and more cloudiness of the aqueous.

Promin blood levels of 8 of the treated animals were determined at the sixth week. In 4 animals, from whom blood was obtained sixteen and one-quarter hours after the last dose of promin, the blood levels ranged from 3.8 to 4.5 mg. per cent, while in 4 from whom blood was obtained five hours after the last feeding of the drug the levels were 6.7 to 7.7 mg. per cent. None of the guinea pigs showed any gross evidence of toxicity from the drug.

TABLE 1

ORIGINAL GROUPS	REGROUPING AFTER 109 DAYS	NUMBER OF ANIMALS IN GROUP	DEGREE OF TUBERCULOSIS				TOTAL DEGREE OF TUBERCULOSIS	RATING* OF EYE	DAYS OF LIFE
			Lungs	Liver	Spleen	Lymph Nodes			
A Nonvaccinated	Nontreated controls	5	4.0	4.0	4.0	4.0	16.0	5.0	82
B Vaccinated controls	Nontreated	9	2.6	3.4	3.5	3.4	12.9	4.7	295
	Treated	9	0.8	0.6	0.8	1.6	3.8	3.7	295
C Vaccinated, treated orally with promin	Treatment discontinued	9	1.9	2.1	2.1	3.0	9.1	4.6	295
	Treatment continued	9	0.5	0.9	0.9	1.3	3.6	3.4	295
D Vaccinated, treated orally and locally with promin	Treatment discontinued	4	2.0	2.3	2.0	2.3	8.6	4.5	295
	Treatment continued	4	0.5	0.0	0.0	1.0	1.5	2.0	295

* Maximum rating 5.

One hundred nine days from the date of infection the surviving animals in groups B, C and D were further divided and treatment changed as follows: Half of group B (vaccinated controls) were started on promin orally, and half continued without treatment. Half of the animals in each of the groups C and D were continued on treatment as previously, and in the remainder of these groups the treatment was discontinued. This was done to ascertain the effect of promin on an infection 109 days old in groups B, C and D, and to observe the course of the disease after treatment was discontinued.

After 295 days all surviving animals were sacrificed. The autopsy findings are summarized in table 1. For the purpose of record and comparison, the in-

volvement of the spleen, liver, lungs, and lymph nodes was noted and individually assigned values were given proportionate to the extent and severity of the tuberculosis. The maximum rating of 4 in any organ was used to indicate wide-spread caseous disease diagnosed by gross inspection. The maximum value of 16 for the animals as a whole signified advanced generalized tuberculosis.

The animals in group A (nonvaccinated controls) all died within eighty-two days of generalized tuberculosis, with complete destruction of the infected eye. The vaccinated untreated animals had a wide-spread chronic type of infection, whereas the treated groups had a significantly less degree of tuberculosis. The animals in group B, whose promin treatment was begun 109 days after infection, showed a definite beneficial effect from this delayed treatment, and those in groups C and D that received drug therapy throughout the course of their disease fared best of all.

DISCUSSION

We have treated experimental ocular tuberculosis in guinea pigs with promin and, although we have not seen any eyes restored to their original appearance, we feel that we have shown sufficient retardation in the progression of the disease to warrant this report. In many of the animals the disease remained localized in the inoculated eye, and showed no macroscopic disease beyond the adjacent post-auricular lymph nodes. The combination of local and oral treatment seems to have offered these animals only slightly more protection than oral administration alone, and that mainly during the first three weeks. It must be remembered that, even though promin is very soluble and we used a 35 per cent solution in the eye, frequent and prolonged contact between the eye and the drug is necessary to obtain an appreciable diffusion through the cornea and the sclera. The solution was dropped into the eye three times daily and the animals were held in position for five minutes each time. This procedure enabled us to obtain levels in the eye of 2 to 5 mg. per cent. We found these levels to be no higher in traumatized eyes than in normal eyes. It is possible that with the application of the drug solution every hour much higher levels can be obtained, thereby increasing the efficacy of the drug upon the local eye lesion.

CONCLUSIONS

1. Promin exerts a definitely beneficial action on the early course of experimental ocular tuberculosis in the vaccinated guinea pig.
2. Those animals in which treatment was continued showed less disease than those taken off the drug after 109 days.
3. The drug produced a marked retardation upon the disease of those vaccinated animals that had treatment delayed for 109 days.
4. The method of eye infection offers a relatively rapid and easily observable method of testing new chemotherapeutic agents for the treatment of tuberculosis.

CONCLUSIONES

1. La promina ejerce un efecto netamente beneficioso sobre la evolución temprana de la tuberculosis ocular experimental en el cobayo vacunado.

2. Los animales en que se continuó el tratamiento mostraron menos enfermedad que aquellos en que se suprimió la medicación al cabo de 109 días.

3. La droga reveló un notable efecto retardador sobre la enfermedad en los animales vacunados en los que se demoró el tratamiento por espacio de 109 días.

4. La técnica de la infección ocular ofrece un método relativamente rápido y fácil de observar para la comprobación de nuevos elementos quimioterapeúticos destinados al tratamiento de la tuberculosis.

REFERENCES

(1) Steenken, W., Jr., Heise, F. H., and Wolinsky, E.: Treatment of experimental tuberculosis in the vaccinated and nonvaccinated guinea pig with promin, Am. Rev. Tuberc., 1943, *48*, 453.

(2) Steenken, W., Jr., and Gardner, L. U.: Vaccinating properties of avirulent dissociates of five different strains of tubercle bacilli, Yale J. Biol. & Med., 1943, *15*, 393.

(3) Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: Promin in experimental tuberculosis: Sodium P,P-diaminodiphenylsulfone-N,N′-didextrose sulfonate, Am. Rev. Tuberc., 1942, *45*, 303.

(4) Feldman, W. H., Mann, F. C., and Hinshaw, H. C.: Promin in experimental tuberculosis: Observation on tuberculous guinea pigs before and after treatment with sodium P,P′-diaminodiphenyl-sulfone-N,N′-didextrose sulfonate (promin), Am. Rev. Tuberc., 1942, *46*, 187.

(5) Feldman, W. H., and Hinshaw, H. C.: Effects of prolonged treatment with sodium P,P-diaminodiphenylsulfone-N,N′-didextrose sulfonate (promin) on subsequent reinfection, Am. Rev. Tuberc., 1945, *51*, 268.

(6) Medlar, E. M., and Sasano, K. T.: Promin in experimental tuberculosis in the guinea pig, Am. Rev. Tuberc., 1943, *47*, 618.

(7) Smith, M. I., Emmart, E. W., and Westfall, B. B.: The action of certain sulfonamides, sulfones and related phosphorus compounds in experimental tuberculosis, J. Pharmacol. & Exper. Therap., 1942, *74*, 163.

(8) Callomon, F. F. T.: New derivatives of diaminodiphenyl-sulfone: Their therapeutic effect on experimental tuberculosis of guinea pigs, Am. Rev. Tuberc., 1943, *47*, 97.

(9) Melville, K. I., and Stehle, R. L.: Chemotherapy in experimental tuberculosis, Canad. J. Research, 1944, *22*, 95.

(10) Steenken, W., Jr.: Unpublished.

Report of the Second Michigan-Wisconsin-Minnesota Regional Therapy Conference

Conference Committee

Dr. John D. Steele, *Chairman*

Dr. Karl H. Pfuetze
Dr. John W. Towey

A second regional conference on tuberculosis therapy was held at the Four Seasons Club near Pembine, Wisconsin, on June 15, 16 and 17, 1945. Michigan was represented by 22 delegates, Wisconsin by 14 and Minnesota by 13. In addition, several observers were present from other states.

Essentially the same differences of opinion in regard to the choice of certain therapeutic measures and in the evaluation of laboratory procedures which had been apparent at last year's conference were still apparent and were observed to be essentially on a regional basis. However, it was agreed that these differences were not as marked and that there had been a definite tendency toward acceptance of other ideas as the result of the previous conference.

Since the report of the 1944 conference (AM. REV. TUBERC., 1944, *50*, 575) contained a digest of opinions expressed in regard to specific procedures, it was agreed that a repetition of these would be superfluous in the present report. However, since the mechanics of the 1945 meeting differed appreciably from those of the 1944 meeting, it was decided that these should be reported in some detail with the hope that the experience gained in the past two years might be of value to those conducting similar future conferences in other regions.

Morning and afternoon sessions of the first two days of the conference were devoted to case presentations. Discussion of each case took place at the time of presentation. Last year the case presentations had been accompanied by little or no discussion at the time of presentation but were re-presented later for discussion. It was agreed that the system used this year was preferable. Mimeographed sheets were distributed to each delegate containing the following data in regard to each patient:

1. Name, age, sex, race.
2. Admission date and classification.
3. Discharge date, classification and reason for discharge.
4. Length of sanatorium stay.
5. Examination of pulmonary secretions including type of examination with results on admission and discharge (or present).
6. Collapse therapy.
7. Important complications.
8. Remarks.

The significant roentgenograms of 75 patients from a representative sanatorium from each state had been prepared for presentation. Four hours were

allotted for the presentation from each state. All cases presented were consecutive admissions starting with January 1, 1943, although the selection of cases varied as noted below.

Dr. John K. Shumate, Lake View Sanatorium, Madison, Wisconsin, presented the majority of his cases which included first admissions only (including a few nontuberculous patients).

Dr. C. J. Stringer, Ingham Sanatorium, Lansing, Michigan, presented the majority of his cases which included only tuberculous patients but included readmissions as well as first admissions.

Dr. G. A. Hedberg and his associates, Drs. Roberts Davies and Samuel T. Sandell, completed the presentation of 75 consecutive first admissions (tuberculous and nontuberculous) to Nopeming Sanatorium, Nopeming, Minnesota.

Even though Drs. Shumate and Stringer did not finish the presentation of 75 cases each, it was agreed that their methods of diagnosis and treatment had been demonstrated adequately. The completion of the presentation of the 75 cases by the Minnesota group in less than their allotted time was due not only to their excellent team-work in making the presentation but also to the fact that their presentation was the third and, therefore, there was less discussion on various controversial issues which had been fully discussed during the two previous presentations.

A vote was taken when there appeared to be any considerable controversy concerning the management of an individual case. Definite regional differences were apparent in some instances when the delegates from each state were called upon to vote separately.

Following the case presentations, the meeting was thrown open for criticisms and suggestions as to the mechanics of this and other proposed regional conferences.

The size of the meeting evoked considerable discussion. (This year's meeting had been limited to 50, exclusive of local physicians, by the regulations of the Office of Defense Transportation.) The attendance at last year's meeting had been 23. It was agreed that an attendance of 50 should probably be the upper limit of such conferences. Even with such a limit, many delegates could not satisfactorily view the roentgenograms presented. This was not considered to be a great disadvantage if the lesions were properly demonstrated by the presenting physician.

A number of suggestions were made as to the possible presentation of groups of admissions, readmissions, resident patients and discharged patients. No definite agreement was reached on this subject. It was agreed, however, that the method of selection of cases for this year's conference was satisfactory in that it gave a good picture of the indications for therapy and the methods of diagnosis employed by each of the three sanatoria making the presentations.

It was unanimously agreed that delegates from the same three states should meet annually in the future in order to take advantage of the frank and friendly discussion which had prevailed at the two meetings so far held. A majority was in favor of presenting specific types of treatment cases, such as thoracoplasties,

pneumothoraces, phrenic paralyses, etc., at next year's meeting as a variation from consecutive case presentations.

During the evening of the second day of the conference, two subjects of unusual interest were presented informally. Dr. Karl Pfuetze, Cannon Falls, Minnesota, reported on the present status of chemotherapy in tuberculosis, including his extensive experience with the use of the sulfone derivatives. His meagre experience with the use of one antibiotic was mentioned.

The second presentation of the evening on the subject of postmortem injection of the pulmonary vascular system, by Dr. W. L. Brosius, Detroit, was illustrated by a series of slides which demonstrated the changes in the vascular system which occur in various pulmonary conditions.

The last morning of the conference was devoted to presentations of a controversial nature by one delegate from each of the three states represented. General discussion followed each presentation.

Dr. G. A. Hedberg, Nopeming, Minnesota, reported on the results of *extrapleural pneumothorax* in 47 patients operated upon since 1939. Forty-one patients had unilateral and 6 bilateral operations. Forty-six operations were performed between 1939 and 1942; 8 from 1943 to 1945. Twenty-three patients are now classified as arrested, 4 as quiescent, 7 as improved, one as unimproved and 7 are dead (the death of one patient being attributed directly to the operation). The sputum was converted in 37 patients.

The important complications were as follows: 4 patients developed an empyema with a bronchopleural fistula, 6 patients had empyemata without fistulae.

Eight patients had subsequent obliteration of their extrapleural spaces by thoracoplasty. The pneumothorax space was converted to an oleothorax in 37 instances.

Dr. Hedberg pointed out that the indications for extrapleural pneumothorax had been modified considerably in the past three years and that many patients in his earlier group would now have had thoracoplasties instead of extrapleural pneumothoraces. This is particularly true in patients with active lesions in the contralateral lung, who were formerly believed to be unsuitable risks for thoracoplasty.

Dr. J. D. Steele, Milwaukee, presented the results of *extrapleural pneumonolysis followed by paraffin filling*, and Dr. John Alexander, Ann Arbor, Michigan, reported on *pneumonectomy and lobectomy in tuberculosis*. These last two presentations follow this report.

Extrapleural Pneumonolysis with Paraffin Filling[1,2]

Present Status

JOHN D. STEELE, Jr.

Extrapleural pneumonolysis with paraffin filling has not been widely accepted for the treatment of pulmonary tuberculosis. This operation has apparently gained the unenviable reputation among a majority of phthisiologists of being frequently complicated by such unpleasant occurrences as expectoration of paraffin, infection of the extrapleural space, extrusion of the paraffin from the wound, migration of the paraffin, and so forth. We believe that these complications occur relatively infrequently and that the advantages of the procedure far outweigh the disadvantages. The success and safety of the operation depend upon strict adherence to the proper indications and to an approved operative technique.

Our present report is based on a group of 39 patients whose operations were performed between December, 1938 and May, 1944. Five patients had bilateral operations; 2 patients had supplementary anterior pneumonolyses. Eight patients operated upon subsequently and 2 other patients who have not been adequately followed have not been included in this report. (No serious complications occurred in these 10 patients.)

The discharge or present status of the 39 patients who form the basis of this report is as follows: 27 were discharged from the sanatorium as apparently arrested (the gastric contents of 25 were negative on repeated cultures; the sputa of the other 2 were negative on culture); 2 were discharged as quiescent (the gastric contents of one and the sputum of the other were positive on culture); 5 are still in residence in the sanatorium (the disease of 3 is active, but the gastric contents of the other 2 are negative on culture); 5 are dead (4 died of progression of their tuberculosis; the tuberculosis of the other was inactive at the time of death from carcinoma of the stomach). Three of the patients discharged as apparently arrested subsequently had reactivitation of their disease. Nineteen of the discharged patients are working.

INDICATIONS

Our indications for extrapleural pneumonolysis with paraffin filling in our present series of patients are demonstrated diagrammatically in figures 1 and 2. We are now limiting the use of this procedure to apical lesions with cavities not over 1.5 cm. in diameter and with surrounding infiltration not over 5 cm.

[1] From the Departments of Surgery, Muirdale Sanatorium, Wauwatosa, Wisconsin and the Marquette University School of Medicine, Milwaukee, Wisconsin.

[2] Read before the Second Michigan-Wisconsin-Minnesota Regional Tuberculosis Therapy Conference, Pembine, Wisconsin, June 17, 1945.

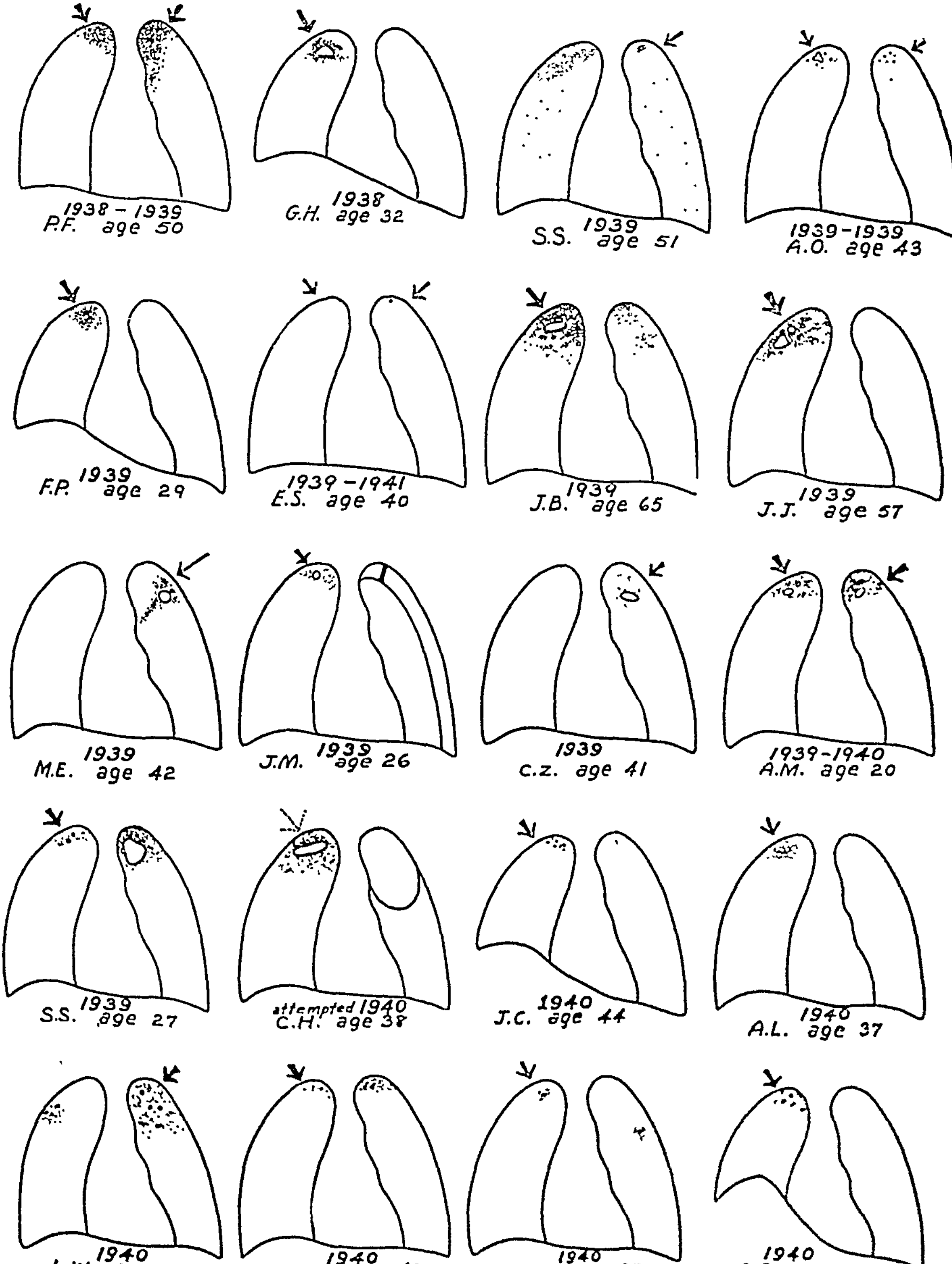


Fig. 1

Figs. 1 and 2. Diagrams illustrating roentgenological appearance of tuberculous lesions for which extrapleural pneumonolyses with paraffin filling were performed. Active disease only is demonstrated. Arrows indicate the side of the operation. Contralateral collapse therapy procedures in effect at the time of the extrapleural pneumonolyses are indicated (phrenic paralyses, intra- and extrapleural pneumothoraces, thoracoplasties).

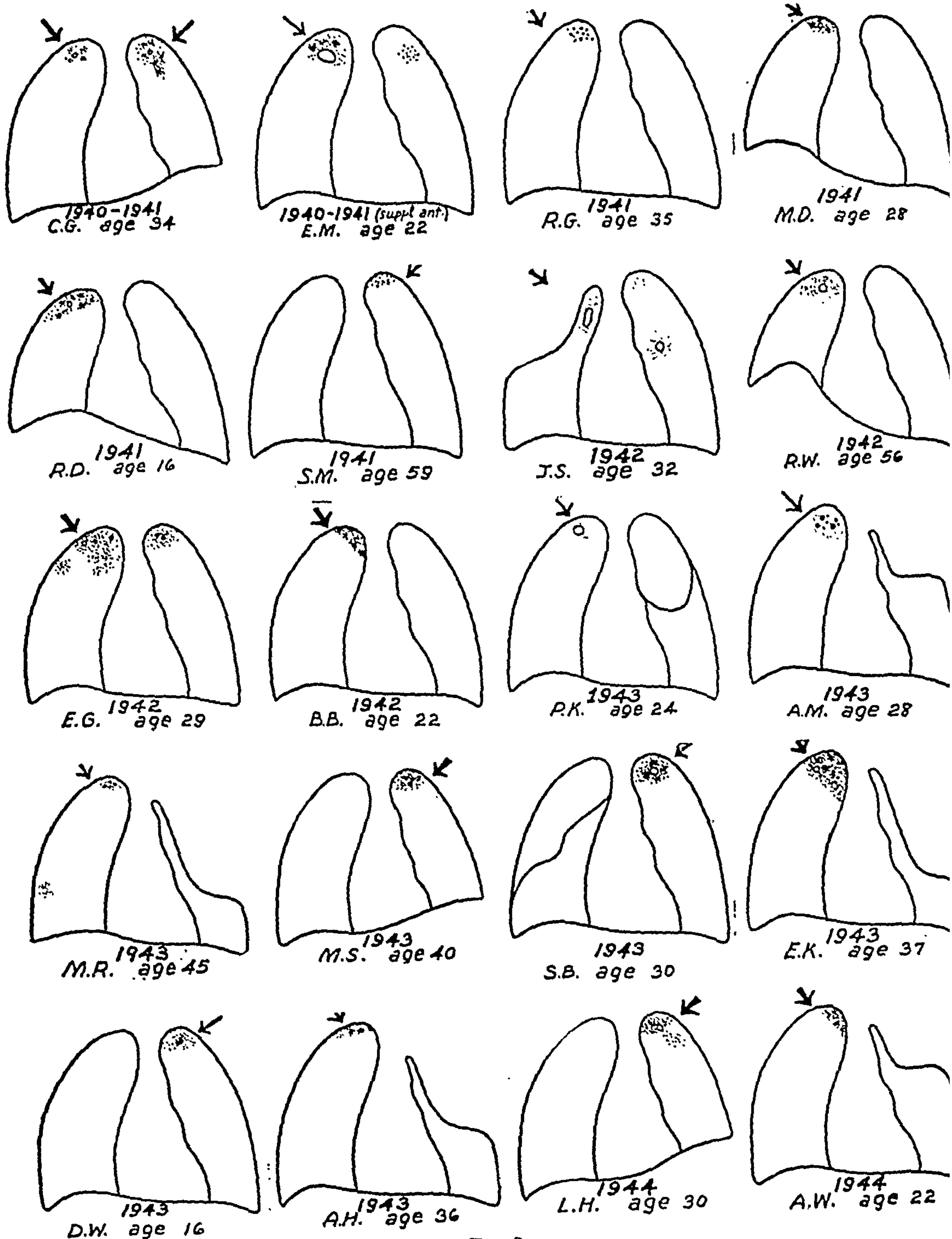

1940-1941 C.G. age 34
1940-1941 (suppl ant.) E.M. age 22
1941 R.G. age 35
1941 M.D. age 28
1941 R.D. age 16
1941 S.M. age 59
1942 J.S. age 32
1942 R.W. age 56
1942 E.G. age 29
1942 B.B. age 22
1943 P.K. age 24
1943 A.M. age 28
1943 M.R. age 45
1943 M.S. age 40
1943 S.B. age 30
1943 E.K. age 37
1943 D.W. age 16
1943 A.H. age 36
1944 L.H. age 30
1944 A.W. age 22

FIG. 2

in diameter. We no longer use the operation as a last resort procedure in preference to thoracoplasty in larger lesions. It will be noted in figure 1 that some of the patients in the early part of our series had larger cavities and more extensive lesions than those in the latter part (figure 2). In a number of our earlier patients, thoracoplasty would have been the operation of choice according to our present standards.

We have found extrapleural pneumonolysis with paraffin filling particularly useful in controlling small apical lesions in the contralateral lung following pneumothorax, extrapleural pneumothorax or thoracoplasty for the lung with the more extensive involvement. In our present series paraffin fillings were used in this manner in conjunction with the following procedures: thoracoplasty (6 patients), contralateral paraffin fillings (5 patients), intrapleural pneumothorax (3 patients) and extrapleural pneumothorax (one patient).

OPERATIVE TECHNIQUE

We think that any beneficial effect which may follow an extrapleural pneumonolysis should be attributed to the relaxation of the portion of the lung which has been freed from the chest wall. When the extrapleural space is filled with lumps of paraffin, the relaxation produced by the pneumonolysis is merely maintained. It is important that the paraffin be introduced gently without pressure; otherwise the pressure of the paraffin on lung tissue may produce necrosis. For this reason we never refer to this operation as a paraffin "pack."

The operative technique for extrapleural pneumonolysis with paraffin filling can be found in detail elsewhere (1, 2, 3). Only a few miscellaneous, more recent details will be given here.

The weight of the paraffin fillings in the present series varied from 120 to 325 g. We now feel that the upper limit of the filling should be 200 g. in small persons and 250 g. in large persons. There is always a great temptation at the time of operation to carry the dissection lower than necessary, particularly if the extrapleural separation is easy. Resection of the third rib instead of the fourth may help to control this overenthusiasm.

We have used general anesthesia for the past three years; prior to this we used local anesthesia.

Cotton suture material has been used exclusively for the past three years with satisfactory results.

The periosteum on the edges of the ribs on either side of the rib defect is freed in order to facilitate closure of the intercostal muscles.

If any free pleural space exists beneath the area of the proposed extrapleural dissection, we perform a poudrage according to the method of Bethune (4) with sterile talcum powder two months prior to the pneumonolysis, because we feel that normal parietal pleura cannot always be freed from the chest wall without tearing.

COMPLICATIONS

Only two serious complications were encountered in our present series. One was a bronchopleural fistula followed by a mixed infection of the extrapleural

space in one of our 3 patients on whom the operation was attempted but not completed because of dense adhesions between the parietal pleura and chest wall. This complication was definitely due to an error in operative technique, as the lung was torn in a desperate attempt to free it from the chest wall. The patient died a year and a half later from progression of her disease. She presented a poor indication for the operation, but at that time we did not believe that she was a suitable thoracoplasty risk. (Case C. H., figure 1, fourth row from top.)

The second serious complication occurred following an attempt to close a tension cavity which remained patent after a thoracoplasty. The paraffin eroded through the cavity wall and had to be removed because of infection three and one-half months later. Cavernostomy would have been the procedure of choice in this case. The patient subsequently died from progression of her disease. (Case J. S., figure 2, second row from top.)

Of the remaining 37 patients, we could find only 4 who presented any complication worthy of note. All had rather marked effusions in the extrapleural space requiring aspiration. The effusion in one patient persisted for seven months and was accompanied by a low grade fever. She is now perfectly well six years after the operation. The effusions of the other 3 patients were transient but required aspiration because of dyspnea. It so happened that these 3 had had phrenic paralyses and had fairly high elevations of their hemidiaphragms at the time of their pneumonolyses. In these 3 patients the amount of paraffin inserted was in excess of that which we now believe adequate.

There was no immediate operative mortality in the entire series.

The absence of late complications in our discharged patients was determined by means of questionnaires.

SUMMARY

Extrapleural pneumonolysis with paraffin filling is a safe, effective operation in the treatment of pulmonary tuberculosis. The success and safety of the operation depend upon strict adherence to the proper indications and to an approved operative technique.

SUMARIO

La neumonolisis extrapleural a base de parafina constituye una operación segura y eficaz para el tratamiento de la tuberculosis pulmonar. El éxito e inocuidad de la misma dependen de la rígida observación de las indicaciones y de una técnica operatoria aceptable.

REFERENCES

(1) McIndoe, R. B., and Alexander, J.: Extrapleural paraffin pneumonolysis for phthisis, Am. Rev. Tuberc., 1934, *24*, 270.
(2) Alexander, J.: The collapse therapy of pulmonary tuberculosis, Charles C Thomas, 1937.
(3) McIndoe, R. B., Steele, J. D., Jr., and Alexander, J.: Extrapleural pneumonolysis with paraffin filling, Am. Rev. Tuberc., 1939, *40*, 243.
(4) Bethune, N.: Pleural poudrage, J. Thoracic Surg., 1935, *4*, 251.

Comments about Pneumonectomy and Lobectomy in Tuberculosis[1]

JOHN ALEXANDER[2]

These comments about total pneumonectomy and lobectomy in tuberculosis necessarily express only tentative opinions because no surgeons, except Overholt and Wilson, have operated upon a large number of patients, and Overholt and Wilson's reported 59 patients were operated upon as recently as between January 1, 1942 and January 1, 1944.

The removal of all the demonstrable tuberculous lesions, or even the principal ones, is an attractive idea. Experience has, however, shown that pulmonary resection for tuberculosis exposes the patient to far greater dangers than does resection for carcinoma or bronchiectasis. For this reason an overwhelming majority of phthisiologists and thoracic surgeons are restricting resection to those patients for whom no other form of treatment is likely to bring about recovery.

CHIEF DANGERS AND DISADVANTAGES OF RESECTION

(*1*) A relatively high death rate within the first two or three years. Overholt and Wilson's deaths in 59 patients were 8, or 13.6 per cent; they state that 6 other patients will die (this would make the mortality 23.7 per cent); 9 other patients have a guarded prognosis. The mortality in Churchill and Sweet's series of 35 Massachusetts General Hospital patients is 11.4 per cent. Six of Robert Janes' 32 resection patients are dead, a percentage of 18.7; some of the 26 living patients are doing badly and some of those having positive sputum are doing well. Herbert Maier has had one death among 18 patients, or 5.5 per cent. Five of Overholt and Wilson's "desperate risk" patients died and 2 of their 47 "reasonable risks." All 8 of Haight and Alexander's total pneumonectomy patients would fall into Overholt and Wilson's "desperate risk" category; 3 are dead and one more will probably die. An encouraging recent development is that Overholt has operated on 27 patients under local anesthesia in the face-down position with only one death and no spread or exacerbation of the tuberculosis.[3]

(*2*) A high percentage of miscellaneous complications: Spread or exacerbation of tuberculosis (23 per cent in Overholt and Wilson's series), tuberculous, or tuberculous and pyogenic, empyema and wound infection, persisting tuberculous ulceration in bronchial stump, bronchopleural fistula, progressive tuberculous bronchitis, respiratory or cardiac insufficiency and tuberculous meningitis.

(*3*) Sacrifice of good, functioning pulmonary tissue when a total pneumonec-

[1] Presented at the Second Michigan-Wisconsin-Minnesota Regional Tuberculosis Therapy Conference, Pembine, Wisconsin, June 17, 1945.

[2] From the Department of Surgery, University of Michigan, Ann Arbor, Michigan.

[3] His later figures are much less favorable (January 10, 1946).

tomy is performed for lesions that do not involve the whole lung. Restriction of the function of the lower lobe by pleural thickening occurs after many upper lobe lobectomies. Reduction in respiratory function from overdistension of the remaining pulmonary tissue probably occurs if a thoracoplasty is not performed in order to prevent this overdistension.

(*4*) Except in cases having only limited parenchymal lesions, "resection" usually implies a total pneumonectomy. Situations usually requiring the removal of a whole lung are: (*a*) in cases having parenchymal lesions in the lower, or lower and middle lobes, an ulcerative or stenotic tuberculous bronchial lesion involving the upper lobe bronchus requires the sacrifice of this lobe even if its parenchyma is not visibly involved; (*b*) even when only an upper-lobe lobectomy is intended before operation, the surgeon may find by palpation at the time of operation a hitherto undiagnosed tuberculous lesion in the apical portion of the lower lobe, or a lesion that has traversed an obliterated fissure to involve the adjacent portion of the lower lobe; either of these situations requires the removal of the lower as well as the upper lobe, unless a "segmental lobectomy" is risked; (*c*) tuberculous bronchitis in the superior dorsal bronchus of the lower lobe may require, in addition to resection of the lower lobe, resection of the middle lobe on the right side, or of the upper lobe on the left side, because of the danger of progression of the tuberculous bronchitis into these lobes, whose bronchial orifices are in close proximity to the orifice of the superior dorsal bronchus of the lower lobe.

INDICATIONS

In my opinion, the most important indications for total pneumonectomy for unilateral tuberculosis and its complications are:

(*1*) Active cavernous tuberculosis with a tight bronchial stenosis at, or proximal to, the upper lobe orifice, with severe coughing and retention of secretions. Such patients are not suitable for thoracoplasty, or an ineffectual thoracoplasty may already have been performed.

(*2*) Disabling symptoms from bronchiectasis and suppurative pneumonitis, with or without bronchial stenosis and with or without active tuberculosis. Thoracoplasty is not suitable for these patients, although one may already have been performed.

(*3*) Multiple residual tuberculous cavities (whether or not tension cavities) after a modern type of thoracoplasty.

Among the important indications for lobectomy (with allowance for section 4 under "Chief Dangers and Disadvantages," above) are:

(*1*) A basal cavity that has not responded to pneumothorax or phrenic paralysis, or both, for which lobectomy may seem, in a particular case, preferable to surgical drainage.

(*2*) A cavity in any lobe that fails to close with pneumothorax or phrenic paralysis, or both, in young children (because of the danger of severe scoliosis after thoracoplasty).

(3) A cavity in any lobe remaining open after a modern type of thoracoplasty in cases in which lobectomy seems preferable to direct, surgical drainage.

(4) A tuberculoma, unsuitable for collapse therapy and causing troublesome symptoms or producing tubercle bacilli in the sputum or gastric contents.

IMPORTANT CONTRAINDICATIONS TO PNEUMONECTOMY OR LOBECTOMY

(1) Insufficient cardiac or respiratory reserve.

(2) Ulcerative tuberculous bronchitis at, near, or proximal to the site at which the bronchus would need to be divided.

(3) Grave extrapulmonary tuberculous or nontuberculous disease.

(4) Tuberculous lesions that are in a part of either lung not to be removed and that are not likely to become healed.

If, as I believe, the late results of pneumonectomy and lobectomy will prove to be far inferior to those of thoracoplasty in cases in which either type of operation might reasonably be used, I strongly recommend that neither pneumonectomy nor lobectomy be used in preference to thoracoplasty in any case unless the indications for resection are clear-cut and unless thoracoplasty is unlikely to succeed.

SUMMARY

1. Total pneumonectomy or lobectomy in tuberculosis is much more dangerous than in carcinoma or bronchiectasis, with reference to both early and late mortality, and serious postoperative complications.

2. At present the indications for resection in tuberculosis should be restricted to those patients for whom the modern type of thoracoplasty and other collapsing operations are unlikely to be effective.

3. The chief indications for total pneumonectomy in predominantly unilateral tuberculosis are: active, cavernous tuberculosis with high-grade bronchial stricture; disabling symptoms from bronchiectasis and suppurative pneumonitis, with or without active tuberculosis; multiple residual tuberculous cavities remaining after a modern thoracoplasty.

4. The chief indications for lobectomy are: a basal cavity remaining open after a trial of phrenic paralysis and pneumothorax and in which lobectomy may, in particular patients, be preferable to surgical drainage; a cavity in any lobe remaining open after a trial of phrenic paralysis and pneumothorax, in young children; a cavity remaining open after a modern thoracoplasty, in which lobectomy seems preferable to surgical drainage; a tuberculoma unsuitable for collapse therapy and producing troublesome symptoms or tubercle bacilli in the sputum or gastric contents.

5. The indications mentioned in the last two paragraphs are based on the assumption that the patients are in suitable condition for the operations, that ulcerative tuberculous bronchial lesions are not present at, near, or proximal to the site of intended division of the bronchus, and that any parenchymal lesions not to be resected are more likely to become healed than to progress.

SUMARIO

1. En la tuberculosis la panneumectomía o lobectomía es mucho más peligrosa que en el carcinoma o la bronquiectasia, tanto en cuanto a la mortalidad inmediata y tardía como a las complicaciones postoperatorias graves.

2. En la actualidad las indicaciones de la resección en la tuberculosis deben limitarse a los enfermos en los que probablemente no darían resultado la toracoplastia de tipo moderno y otras operaciones de colapso.

3. En la tuberculosis de predominio unilateral las principales indicaciones de la panneumectomía son: tuberculosis cavernosa, activa, con estenosis bronquial acentuada; síntomas incapacitantes debidos a bronquiectasia y neumonitis supurada, con o sin tuberculosis; múltiples cavernas tuberculosas subsistentes después de una toracoplastia moderna.

4. Las principales indicaciones de la lobectomía son: una caverna basal que permanece abierta despues de ensayar la parálisis del frénico y el neumotórax, y en la cual, en ciertos enfermos, la lobectomía puede resultar preferible al drenaje quirúrgico; una caverna en cualquier lóbulo, en los niños pequeños, que permanece abierta después de ensayar la parálisis del frénico y el neumotórax; una caverna que permanece abierta después de una toracoplastia moderna, y en la cual la lobectomía parece preferible al drenaje quirúrgico; un tuberculoma impropio para la colapsoterapia que produce síntomas molestos o bacilos tuberculosos en el esputo o contenido gástrico.

5. Las indicaciones mencionadas en los dos últimos párrafos básanse en la suposición de los que los enfermos se encuentran en estado apropiado para la intervención, de que no existen lesiones tuberculosas ulceradas en los bronquios inmediatos, cercanos o proximales al sitio de la propuesta división del bronquio, y de que hay mayores probabilidades de cicatrización que de agravación en toda lesión parenquimatosa que no va a resecarse.

NOTICE

The 1946 meeting of the American Association for Thoracic Surgery will be held in Detroit, May 29, 30 and 31, 1946, with headquarters at the Hotel Statler.

Dr. Edward J. O'Brien, 207 David Whitney Building, is Chairman of the local Committee on Arrangements. Secretary of the Association is Lt. Col. Richard H. Meade, Jr., M.C., Kennedy General Hospital, Memphis 15, Tennessee.

SPIROMETRIC AND BRONCHOSPIROMETRIC STUDIES IN THORACOPLASTY[1]

GEORGE C. LEINER

Following thoracoplasty, total pulmonary volumes and functions are diminished (McIntosh (1); Lindskog and Friedman (2); Pinner (3); Kaltreider, Fray and Philipps (4); Harter, Overholt and Perkin (5); Lambert, Berry, Cournand and Richards (6); Schmidt and Gaubatz (7); Cournand and Richards (8); Warring (16)). The reserve air shows the most extensive reduction. The maximum breathing capacity may occasionally increase (Cournand and Richards (8)).

The effect of thoracoplasty on individual lung functions has been studied in only a few cases. Björkman (9) and Jacobaeus (10) reported bronchospirometric examinations on 3 patients before and after thoracoplasty: they noticed that in the thoracoplasty lung a certain amount of restitution takes place; that the healthy lung, too, diminishes in volume due to displacement of the mediastinum; that in one patient the thoracoplasty lung showed functional improvement after the operation. Leiner, Pinner and Zavod (11) analyzed in detail the bronchospirometric findings in 3 patients before and after thoracoplasty. Vaccarezza, Lanari, Bence and Labourt (12) did a few bronchospirometric studies in tuberculous patients treated with various forms of collapse therapy. Pinner, Leiner and Zavod (13), who did bronchospirometry in 11 patients who had undergone thoracoplasty, came to the conclusion that thoracoplasty lungs, if not complicated by diaphragmatic paralysis, participate to a considerable degree in respiration.

METHOD

The methods used in this study were exactly the same as those described in a previous paper on pneumothorax (Leiner (14)).

RESULTS

Spirometric and bronchospirometric examinations were done in 26 patients (16 males and 10 females) before and after thoracoplasty. The thoracoplasties were made in two to three stages, and four to eight ribs were removed. The first functional examination was done a few days before the operation, the second examination in most cases (tables 7, 8, and 9 disclose the details) several months after the last surgical procedure when the patients were believed to have fully recovered from the operation and were completely adjusted to the changed respiratory mechanism under thoracoplasty.

Spirometry: The spirometric findings before and after thoracoplasty are shown in tables 1 to 3. The extent of the thoracoplasty was four ribs in one patient (no. 275), five ribs in 6 patients, six ribs in 9 patients, seven ribs in 9 patients,

[1] From the Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases, New York, New York.

eight ribs in one patient (no. 115). The patients in each group were very different in their pulmonary status and the groups are small; therefore it did not seem justified to present the average for each group separately. The roentgenological findings in each patient are summarized in tables 7 to 9.

TABLE 1

Spirometry before and after four- or five-rib thoracoplasty

Patient number / Sex and Age		331 M 35	45 M 45	55 M 35	61 M 31	311 F 32	350 F 43	329 M 44
O_2 intake in cc.	before	231	225	300	253	183	250	239
	after	229	212	270	201	165	212	206
B M R in per cent	before	−2	−4	+3	+15	−6	+7	−4
	after	−4	−13	−1	−6	−9	±0	−20
Minute volume in cc.	before	8,870	5,760	6,290	7,140	5,980	8,400	9,620
	after	7,610	5,650	8,230	7,790	5,870	8,230	7,140
Tidal air in cc.	before	474	303	443	416	332	420	808
	after	346	257	549	410	255	412	714
Respirations per minute	before	19	19	14	16	18	20	12
	after	22	22	15	19	23	20	10
Ventilation equivalent in liters	before	3.3	2.2	1.8	2.4	2.8	2.8	3.5
	after	2.8	2.3	2.6	3.3	3.1	2.9	3.0
Vital capacity in cc.	before	3,580	1,080	3,460	2,310	1,820	3,150	3,000
	after	2,780	1,260	3,290	2,070	1,430	2,780	2,320
Reserve air in cc.	before	518	145	414	991	269	331	808
	after	414	83	414	683	311	166	808
Complementary air in cc.	before	2,588	632	2,603	900	1,219	2,399	1,384
	after	2,020	920	2,327	977	861	2,202	798
Maximum breathing capacity in liters	before	83.1	31.8	67.6	26.3	38.8	63.6	73.9
	after	63.1	30.2	71.4	35.1	38.4	50.9	50.5
$\frac{\text{Maximum br. cap.}}{\text{Minute volume}}$	before	9.6	5.5	10.9	3.7	6.5	7.6	7.6
	after	8.5	5.3	8.7	4.5	6.5	6.2	7.1

After a four or five-rib thoracoplasty (table 1) oxygen intake and basal metabolic rate dropped in all cases, significantly however only in 2 cases (no. 61 and no. 329). The slight decrease of the basal metabolic rate following collapse therapy has been pointed out before (15). The minute volume decreased in 5 cases and increased in 2 cases. The tidal air decreased in all but one case. The respiratory rate increased in the majority of the cases; the ventilation equivalent

showed changes to either side. The vital capacity dropped in all cases but one (46); the increase in the latter was due to the increase of vital capacity on the contralateral side brought about by a reëxpanded pneumothorax lung. The reserve air showed changes to either side. The complementary air dropped in

TABLE 2

Spirometry before and after six-rib thoracoplasty

Patient number / Sex and age		59 F 28	114 F 18	137 M 39	151 M 36	152 M 27	156 M 28	223 M 32	298 M 21	315 F 43
O_2 intake in cc.	before	197	184	191	211	231	226		260	203
	after	189	184	246	213	264	214	220	262	201
B M R in per cent	before	+2	−8	−23	−15	−22	−16		−7	−2
	after	±0	−5	+1	−11	−8	−23	−11	−7	±0
Minute volume in cc.	before	6,140	5,100	8,230	7,770	8,070	6,480	6,750	6,420	5,320
	after	5,930	5,270	9,080	12,620	11,520	5,210	6,970	7,920	7,370
Tidal air in cc.	before	323	319	457	598	620	405	519	642	355
	after	370	293	378	842	768	401	436	609	335
Respirations per minute	before	18	16	18	13	13	16	13	10	15
	after	12	18	24	15	15	13	16	13	22
Ventilation equivalent in liters	before	2.6	2.4	3.8	3.1	3.0	2.4		2.1	2.3
	after	2.7	2.5	3.1	5.1	3.7	2.1	2.7	2.6	3.2
Vital capacity in cc.	before	1,860	2,110	2,530	3,130	3,980	2,550	4,080	4,620	3,210
	after	1,140	1,550	1,950	2,710	2,960	2,750	2,820	3,520	1,840
Reserve air in cc.	before	166	207	331	414	311	290	1,242	1,036	559
	after	124	207	518	166	290	145	414	476	228
Complementary air in cc.	before	1,371	1,584	1,742	2,118	3,049	1,855	2,319	2,942	2,296
	after	646	1,050	1,054	1,702	1,902	2,204	1,970	2,435	1,277
Maximum br. cap. in liters	before	36.4	32.1	45.6	47.3	65.9	47.6	51.6	93.3	71.4
	after	38.4	25.0	44.6	70.3	58.2	57.1	54.9	64.8	44.3
$\frac{\text{Maximum br. cap.}}{\text{Minute volume}}$	before	5.9	6.3	5.5	6.0	8.1	7.3	7.6	14.5	13.4
	after	6.5	4.7	4.9	5.5	5.0	10.9	7.9	8.2	6.0

most cases; in case 46 it increased in conformity with the vital capacity. Maximum breathing capacity and $\frac{\text{Maximum breathing capacity}}{\text{Minute volume}}$ decreased in most cases. In one case (no. 61) there was an increase in these figures; in this patient, in whom the preoperative values had been low, the thoracoplasty achieved a partial collapse only of the upper third of the left lung.

After a six-rib thoracoplasty (table 2) oxygen intake and basal metabolic rate

showed changes to either side; the abnormal low basal metabolic rate before the operation in 2 cases (no. 137 and no. 152) could not be explained. Minute volume and tidal air showed changes to either side. The respiratory rate increased

TABLE 3

Spirometry before and after seven- or eight-rib thoracoplasty

Patient number / Sex and Age		50 M 29	51 F 37	215 F 34	274 F 41	21 F 32	67 M 39	301 M 36	314 M 25	338 M 36	115 F 39
O_2 intake in cc.	before	215	206	184	203	193	239	326	270	215	187
	after	189	191	228	193	179	240	328	256	196	177
B M R in per cent	before	−10	−5	−13	−1	−4	−6	+18	±0	−5	−4
	after	−19	−9	+7	−3	−7	−2	+23	−4	−14	−8
Minute volume in cc.	before	5,900	6,000	6,000	6,200	8,200	8,200	9,000	4,900	8,500	4,800
	after	5,500	5,900	5,500	5,400	7,200	8,800	7,800	7,400	7,800	5,200
Tidal air in cc.	before	424	498	332	388	433	549	528	380	423	281
	after	422	345	343	340	288	488	456	436	357	274
Respirations per minute	before	14	12	18	16	19	15	17	13	20	17
	after	13	17	16	16	25	18	17	17	22	19
Ventilation equivalent in liters	before	2.4	2.5	2.8	2.8	3.7	3.0	2.4	1.6	3.4	2.2
	after	2.5	2.6	2.1	2.4	3.5	3.2	2.0	2.5	3.5	2.6
Vital capacity in cc.	before	2,630	2,070	2,840	2,150	1,410	2,130	3,810	2,220	2,630	1,950
	after	2,280	1,260	2,070	1,370	1,040	1,660	2,820	1,620	2,090	1,390
Reserve air in cc.	before	725	207	828	456	124	249	787	207	621	426
	after	368	166	331	166	166	0	497	0	372	166
Complementary air in cc.	before	1,481	1,365	1,680	1,306	853	1,332	2,495	1,633	1,586	1,243
	after	1,490	749	1,396	864	586	1,172	1,867	1,184	1,361	950
Maximum br. cap. in liters	before	51.6	25.0	46.8	43.9	27.4	49.4	94.2	76.8	36.2	47.8
	after	43.9	22.0	60.4	33.7	26.6	49.4	69.8	51.6	41.7	43.9
$\frac{\text{Maximum br. cap.}}{\text{Minute volume}}$	before	8.7	4.2	7.8	7.1	3.1	6.0	10.0	15.6	4.3	10.0
	after	8.0	3.7	11.0	6.2	3.7	5.7	9.0	7.0	5.3	8.4

in all but 2 cases. Reserve air and complementary air became smaller in most cases. Maximum breathing capacity and $\frac{\text{Maximum breathing capacity}}{\text{Minute volume}}$ decreased more frequently than they increased.

After a seven or eight-rib thoracoplasty (table 3) oxygen intake and basal metabolic rate dropped in most cases. No explanation could be given for the significant rise in one case (no. 215). The minute volume showed changes to

either side. The tidal air usually decreased. The respiratory rate showed more often a tendency to increase. The ventilation equivalent showed changes to either side. Vital capacity and reserve air dropped in all cases, the complementary air in all but one. Maximum breathing capacity and

$$\frac{\text{Maximum breathing capacity}}{\text{Minute volume}}$$ showed changes to either side, but decreased more

frequently than not. From the clinical and roentgenological changes after thoracoplasty it is not possible to explain why the functional changes were different in different patients.

TABLE 4

Spirometry before and after thoracoplasty

Average, maximum and minimum data

		O_2 intake in cc.	B M R in per cent	Minute volume in cc.	Tidal air in cc.	Respirations per minute	Ventilation equivalent in liters	Vital capacity in cc.	Reserve air in cc.	Complementary air in cc.	Maximum breathing capacity in liters	Maximum br. cap. / Minute volume
Number of patients...		25	25	26	26	26	25	26	26	26	26	26
Average	before...	225	−4	6,930	450	16	2.7	2,710	487	1,768	52.9	7.7
	after.....	219	−6	7,270	428	18	2.9	2,110	295	1,383	47.7	6.7
Highest	before...	326	+18	9,690	808	20	3.8	4,620	1,242	3,049	94.1	15.6
	after.....	328	+23	12,620	842	25	5.1	3,520	808	2,435	71.4	11.0
Lowest	before...	183	−23	4,780	281	10	1.6	1,080	124	632	25.0	3.1
	after.....	166	−23	5,210	255	10	2.0	1,040	0	586	22.0	3.7

TABLE 5

Frequency of changes in total lung functions following thoracoplasty

	O_2 intake	B M R	Minute volume	Tidal air	Respirations per minute	Ventilation equivalent	Vital capacity	Reserve air	Complementary air	Maximum breathing capacity	Maximum br. cap. / Minute volume
Increase.....	3	3	8	5	17	9	1	3	2	4	5
Unchanged...	19	20	13	10	5	9	2	4	4	9	9
Decrease.....	3	2	5	11	4	7	23	19	20	13	12

Table 4 gives the average, maximum and minimum data for all spirometric studies before and after thoracoplasty. In a different way, the findings are summarized in table 5. Those in which the pre- and postoperative figures differ by less than 10 per cent are classed as unchanged.

We see that oxygen intake and basal metabolic rate showed a slight tendency to decrease but remained unchanged in the majority of the cases. The average minute volume increased slightly. As the respiratory rate increased at the same time, the average tidal air decreased, and in single patients it decreased more often than it increased. With a decreasing oxygen intake and an increasing minute volume, the ventilation equivalent increased slightly. However, in 7 cases there was a decrease of the ventilation equivalent, indicating an improvement of the respiratory efficiency. All the changes mentioned above were very small and there was no significant difference between more or less extensive thoracoplasties.

The average vital capacity dropped by approximately 22 per cent. In 23 cases it decreased; in only one it increased after a five-rib thoracoplasty. The more extensive the thoracoplasty, the greater was the drop of the vital capacity in average. All the subdivisions of the vital capacity behaved in a similar way, with the reserve air affected most markedly; its average dropped by about 40 per cent. The reserve air also showed definitely an increased drop with an increase of number of ribs removed. The average decrease of the complementary air was 22 per cent. These results correspond well with the observations of Cournand and Richards (8), who found that a correlation existed between the number of ribs resected and the decrease in vital capacity. Table 12 discloses that the tidal air is a larger portion of the vital capacity after thoracoplasty than before, whereas reserve air and complementary air are relatively slightly smaller.

The average maximum breathing capacity decreased by about 10 per cent; only 13 out of 26 cases showed a decrease, whereas in 4 cases an increase was seen.

The changes of the factor $\frac{\text{Maximum breathing capacity}}{\text{Minute volume}}$ were similar. Cournand and Richards (8) have pointed out that no correlation existed between the number of ribs resected and the ratio

$$\frac{\text{Maximum breathing capacity after thoracoplasty}}{\text{Maximum breathing capacity before thoracoplasty}}$$

The changes of maximum breathing capacity and $\frac{\text{Maximum breathing capacity}}{\text{Minute volume}}$ are shown in an additional table (table 6) because we believe that these data are the most significant of all indicating respiratory function. It shows how little this function is affected in average, how frequently there are no changes or even increases, indicating functional improvement in spite of or due to the operation.

Bronchospirometry: Of our 26 patients, 12 received thoracoplasties on the right side and 14 on the left.

The bronchospirometric findings for each lung are presented in tables 7 to 9.

After a four or five-rib thoracoplasty (table 7) oxygen intake decreased in the thoracoplasty lung. In one case (no. 46) in which it was very low before the operation there was no further decrease. On the contralateral side there was an increase in all cases. Minute volume and tidal air showed changes to either side

in both lungs. There was a remarkable drop of the ventilation equivalent in the case which had the extremely poor function before thoracoplasty. The vital capacity dropped or remained unchanged on the operated side, and showed changes in either direction on the contralateral side. Reserve air and complementary air showed, in both lungs, changes to either side.

After a six-rib thoracoplasty (table 8) the oxygen intake showed a tendency to decrease on the operated side and a tendency to increase on the contralateral side. Minute volume and tidal air showed, in both lungs, changes to either side, as did the ventilation equivalent. The vital capacity decreased in all cases on the thoracoplasty side and showed changes in either direction on the contralateral side. Reserve air and complementary air decreased in all thoracoplasty lungs and showed changes in either direction in the contralateral lung.

TABLE 6

Change of maximum breathing capacity and $\dfrac{\textit{Maximum breathing capacity}}{\textit{Minute volume}}$ *caused by thoracoplasty*

FOUR- OR FIVE-RIB THORACOPLASTY			SIX-RIB THORACOPLASTY			SEVEN- OR EIGHT-RIB THORACOPLASTY		
Case	Maximum br. cap. change in per cent	Max. br. cap./Minute volume change in per cent	Case	Maximum br. cap. change in per cent	Max. br. cap./Minute volume change in per cent	Case	Maximum br. cap. change in per cent	Max. br. cap./Minute volume change in per cent
275	−24	−12	59	+6	+10	50	−15	−8
46	−4	−4	114	−22	−25	51	−12	−12
79	+6	−20	137	−2	−11	215	+29	+41
61	+33	+22	151	+49	−8	274	−23	−13
283	−1	±0	152	−12	−38	21	−22	+19
300	−20	−18	156	+20	+50	67	±0	−5
329	−32	−7	223	+6	+4	301	+26	−10
			298	−31	−43	314	−33	−45
			315	−38	−55	338	+15	+23
						115	−8	−16
Average....	−6	−6		−14	−13		−8	−3

After a seven or eight-rib thoracoplasty (table 9) the oxygen intake decreased in the thoracoplasty lung in all cases but one in which it had been low before the operation. In the contralateral side changes in either direction were observed. The minute volume showed changes to either side in both lungs. The tidal air decreased in most cases on the thoracoplasty side and showed changes in either direction on the contralateral side. Vital capacity, reserve air and complementary air decreased on the thoracoplasty side and, with one exception, on the contralateral side; the vital capacity decreased also in all but one case; reserve air and complementary air showed changes in either direction.

The findings for all cases are summarized in table 10. In order to show more clearly the changes following thoracoplasty, they were calculated in per-

TABLE 7

Bronchospirometry before and after four- or five-rib thoracoplasty

PATIENT NUMBER			273	45	72	61	231	300	329
Interval between last stage and bronchospirometry			4 mos.	5 wks.	5 mos.	4 mos.	3 mos.	7 mos.	6 mos.
Side			Left	Left	Right	Left	Right	Left	Left
Thoracoplasty lung	O_2 intake in cc.	before	95	24	145	76	98	100	124
		after	143	24	180	62			69
	Minute volume in cc.	before	5,930	2,510	4,160	4,910	3,910	4,010	4,860
		after	5,210	550	4,500	4,310	4,670	6,310	3,890
	Tidal air in cc.	before	246	100	231	183	145	167	285
		after	186	26	300	190	145	287	229
	Ventilation equivalent in liters	before	5.4	10.3	2.5	5.6	3.4	3.4	3.8
		after	3.1	1.9	2.1	6.8			4.8
	Vital capacity in cc.	before	1,570	250		460	770	1,160	1,200
		after	950	250	1,370	460	500	1,020	910
	Reserve air in cc.	before	311	62			269	104	414
		after	456	21	497	166	145	207	311
	Complementary air in cc.	before	1,013	88			356	889	501
		after	308	203	573	104	200	526	370
	Respirations per minute	before	24	25	18	27	27	24	17
		after	28	21	15	26	30	22	17
Contralateral lung	O_2 intake in cc.	before	152	238	157		118	201	194
		after	239	245	210	250			248
	Minute volume in cc.	before	7,680	6,400	4,210		3,570	5,650	6,460
		after	6,810	4,160	4,940	6,040	4,670	7,440	6,370
	Tidal air in cc.	before	320	256	234		132	236	380
		after	243	198	329	232	155	338	374
	Ventilation equivalent	before	4.4	2.3	2.3		2.6	2.4	2.9
		after	2.4	1.4	2.0	2.1			2.2
	Vital capacity in cc.	before	1,860	750		950	580	2,200	1,660
		after	1,760	1,200	1,840	1,370	810	1,490	1,550
	Reserve air in cc.	before	414	104			207	414	580
		after	663	207	621	787	249	352	746
	Complementary air in cc.	before	1,126	390			241	1,550	700
		after	854	795	890	351	406	800	430
	Roentgenological findings		Minimal fibrosis in apex	Small calcific deposits	Normal	Minimal fibrosis in apex	Normal	Minimal fibrosis in apex	Minimal fibrosis in apex

TABLE 8

Bronchospirometry before and after six-rib thoracoplasty

Patient number			59	114	137	151	152	156	223	298	315
Interval betwen last stage and bronchospirometry			2½ mos.	7 mos.	5 mos.	3 mos.	3 mos.	8 mos.	4 mos.	6 mos.	5 mos.
Side			Right	Left	Right	Left	Right	Left	Right	Left	Right
Thoracoplasty lung	O_2 intake in cc.	before	99	95	68	95	218	64		195	112
		after	74	57		69	156	65	130		
	Minute volume in cc.	before	2,720	3,860	4,500	5,650	6,040	5,440		5,490	4,940
		after	3,930	2,200	2,200	4,940	6,590	2,740	5,490	4,390	7,110
	Tidal air in cc.	before	91	241	173	246	431	302		323	198
		after	157	100	73	247	347	131	305	314	254
	Ventilation equivalent in liters	before	2.3	3.5	5.7	5.1	2.4	7.1		2.4	3.8
		after	4.6	3.3		6.1	3.6	3.6	3.6		
	Vital capacity in cc.	before	990	830	790	870	1,930	1,350	1,700	1,760	1,370
		after	370	410	500	770	1,280		1,010	1,040	460
	Reserve air in cc.	before	518	83	269	207	414	249		207	331
		after	41	41	104	104	269		124	62	
	Complementary air in cc.	before	381	506	348	417	1,085	799		1,230	841
		after	172	269	323	419	664		581	664	
	Respirations per minute	before	30	16	26	23	14	18		17	25
		after	25	22	30	20	19	21	18	14	28
Contralateral lung	O_2 intake in cc.	before	151	172	238	278	158	206		188	146
		after	159	178		224	216	186	130		
	Minute volume in cc.	before	5,870	3,180	6,150	5,650	6,040	5,820		6,310	5,210
		after	4,310	4,610	6,040	6,590	6,590	4,390	6,040	5,870	5,760
	Tidal air in cc.	before	196	199	236	246	431	323		371	209
		after	172	210	201	329	347	209	335	419	206
	Ventilation equivalent in liters	before	3.3	1.6	2.2	1.8	3.3	2.4		2.9	3.1
		after	2.5	2.2		2.5	2.6	2.0	3.9		
	Vital capacity in cc.	before	540	1,140	1,530	1,910	1,950	1,950	1,860	2,420	1,860
		after	830	1,080	1,350	1,930	1,740		1,660	2,200	1,120
	Reserve air in cc.	before	207	113	518	950	414	518		518	518
		after	124	124	414	580	559		414	746	
	Complementary air in cc.	before	137	828	776	714	1,105	1,109		1,531	1,133
		after	534	746	735	1,021	834		911	1,035	
	Roentgenological findings		Normal	Fibrosis in apex	Disseminated fibrocalcific lesions throughout	Normal	Few Calcific nodules subclavicular	Normal	Normal	Normal	Normal

TABLE 9

Bronchospirometry before and after seven- or eight-rib thoracoplasty

PATIENT NUMBER			50	51	215	274	21	67	301	314	338	115
Interval between last stage and bronchospirometry			2 mos.	7 mos.	4 mos.	3 mos.	14 mos.	8 mos.	4 mos.	7 mos.	5 mos.	11 mos.
Side			Right	Right	Right	Left	Left	Left	Right	Left	Left	Right
Thoracoplasty lung	O_2 intake in cc.	before	74	92	127	83	65	150	210	94	54	97
		after	62	26	100	65		52	141		69	84
	Minute volume in cc.	before	4,040	2,690	3,620	3,840	3,550	5,100	4,940	4,170	2,670	4,290
		after	2,000	1,900	3,700	3,370	3,680	1,650	6,530	3,840	4,090	3,460
	Tidal air in cc.	before	288	337	181	154	161	300	206	245	103	165
		after	154	127	161	135	147	92	233	154	241	119
	Ventilation equivlent in liters	before	4.7	2.5	2.5	4.0	4.7	2.9	2.1	3.8	1.2	3.8
		after	2.8	6.3	3.2	4.4		2.6	4.0		1.1	3.5
	Vital capacity in cc.	before	950	620	1,140	750	500		1,350	660	850	700
		after	500	190	700	350		460	1,410	370	700	370
	Reserve air in cc.	before	456	62	456	373	0		373	83	331	266
		after	160	21	124	41		0	104	83	83	83
	Complementary in cc.	before	206	221	503	223	339		771	332	416	269
		after	186	42	415	174		368	1,073	133	376	168
	Respirations per minute	before	14	8	20	25	22	17	24	17	26	26
		after	13	15	23	25	25	18	28	25	17	29
Contralateral lung	O_2 intake in cc.	before	260	231	173	151	145	226	191	290	216	122
		after	197	218	205	242		240	144		174	149
	Minute volume in cc.	before	3,550	5,650	4,060	4,390	5,540	3,710	4,940	5,490	6,400	3,580
		after	3,950	5,600	4,510	5,980	6,590	7,070	5,440	7,300	5,200	3,840
	Tidal air in cc.	before	254	707	203	176	252	218	206	323	246	138
		after	304	373	196	239	263	393	194	292	306	132
	Ventilation equivalent in liters	before	1.2	2.1	2.1	2.5	3.3	1.4	2.3	1.6	2.5	2.5
		after	1.7	2.2	1.9	2.1		2.5	3.3		2.6	2.2

TABLE 9—*Continued*

		50	51	215	274	21	67	301	314	338	115
Patient number		50	51	215	274	21	67	301	314	338	115
Interval between last stage and bronchospiroma		2 mos.	7 mos.	4 mos.	3 mos.	14 mos.	8 mos.	4 mos.	7 mos.	5 mos.	11 mos.
Side		Right	Right	Right	Left	Left	Left	Right	Left	Left	Right
Contralateral lung: Vital cap. in cc.	before	1,370	1,450	1,930	1,470	1,010		1,680	1,330	1,700	1,020
	after	1,620	1,240	1,530	1,060		1,330	1,350	1,060	1,470	720
Reserve air in cc.	before	414	290	621	725	166		414	166	621	359
	after	529	373	497	352		414	83	476	497	331
Complementary air in cc.	before	702	453	1,110	569	592		1,060	841	833	518
	after	787	494	837	469		523	1,073	292	667	257
Roentgenological findings		Normal	Normal	Normal	Slight apical fibrosis	A few small fibrocalcific scattered lesions	Diffuse nodular disseminated lesions	Many small calcific nodules throughout upper lobe	Diffuse fibrosis and moderate emphysema throughout upper third	Moderate fibrosis of upper lobe	Moderate fibrotic strands in apex

centage of the total pulmonary function, the total pulmonary function being determined by adding the function on both sides. (For details see Leiner (14).)

The thoracoplasty lung showed the following changes: The average oxygen intake decreased by about 20 per cent; the minute volume by 10 per cent; the tidal air by about 20 per cent. The slight decrease of the ventilation equivalent, indicating an improvement of the pulmonary efficiency following thoracoplasty, seems noteworthy. The vital capacity dropped by about 35 per cent, the reserve air by about 55 per cent, the complementary air by about 40 per cent. The decrease of the vital capacity and its subdivisions showed some relation to the extent of the thoracoplasty.

Table 12 reveals that, among the subdivisions of the vital capacity, the reserve air showed a considerable drop in relation to the vital capacity, the tidal air a corresponding increase, with the complementary air remaining practically unchanged.

The contralateral lung compensated by an increase in the oxygen intake, brought about only partly by an increase in the minute volume. The ventilation equivalent, therefore, decreased very little. The vital capacity and its sub-

TABLE 10

Bronchospirometry before and after thoracoplasty (four to eight ribs)
Average, maximum and minimum data

		Thoracoplasty lung							Respirations per minute	Contralateral lung						
		O_2 intake in cc.	Minute volume in cc.	Tidal air in cc.	Ventilation equivalent in liters	Vital capacity in cc.	Reserve air in cc.	Complementary air in cc.		O_2 intake in cc.	Minute volume in cc.	Tidal air in cc.	Ventilation equivalent in liters	Vital capacity in cc.	Reserve air in cc.	Complementary air in cc.
Number of patients..		18	25	25	18	22	19	19	25	17	24	24	17	21	19	19
Average	before..	107	4,310	220	4.1	1,030	277	513	21	193	5,230	271	2.4	1,530	424	799
	after....	87	3,870	182	4.0	660	128	305	22	204	5,580	268	2.3	1,370	416	688
Highest	before..	218	6,010	431	10.3	1,930	518	1,230	30	278	7,680	707	4.4	2,420	950	1,550
	after....	180	7,110	347	6.8	1,410	456	1,073	30	248	7,440	419	3.3	1,620	746	1,073
Lowest	before..	24	2,510	91	2.1	250	62	88	8	122	3,570	132	1.2	540	104	137
	after....	24	550	26	1.9	100	21	42	13	144	3,840	132	1.4	720	83	257

TABLE 11

Frequency of relative changes in the functions of each lung following thoracoplasty (four to eight ribs)

	Thoracoplasty lung						Contralateral lung					
	O_2 intake	Minute volume, Tidal air	Ventilation equivalent	Vital capacity	Reserve air	Complementary air	O_2 intake	Minute volume, Tidal air	Ventilation equivalent	Vital capacity	Reserve air	Complementary air
Increase............	1	4	8	2	2	4	9	11	6	14	14	7
Unchanged..........	7	8	3	2	1	6	8	10	4	5	2	10
Decrease............	9	12	7	16	15	8	0	3	7	1	2	1

TABLE 12

Averages of subdivisions of vital capacity in per cent of vital capacity, before and after four- to eight-rib thoracoplasty

		Spirometry			Thoracoplasty lung			Contralateral lung		
		Tidal air	Reserve air	Complementary air	Tidal air	Reserve air	Complementary air	Tidal air	Reserve air	Complementary air
Average	before............	17	17	66	23	29	48	19	29	52
	after...............	21	15	64	31	20	49	20	31	49

divisions decreased somewhat, much less of course than on the thoracoplasty side, so that they showed a relative increase, as compared with the other side (table 11). The relation of tidal air, reserve air and complementary air to each other and to the vital capacity remained practically unchanged (table 12).

One typical case will be presented in detail in order to illustrate better the effects of a thoracoplasty on pulmonary functions.

The patient, no. 274, E. G., was a 41 year old woman. The onset of her disease was in 1931 with a hemoptysis. A left pneumothorax was induced in 1931 and abandoned in

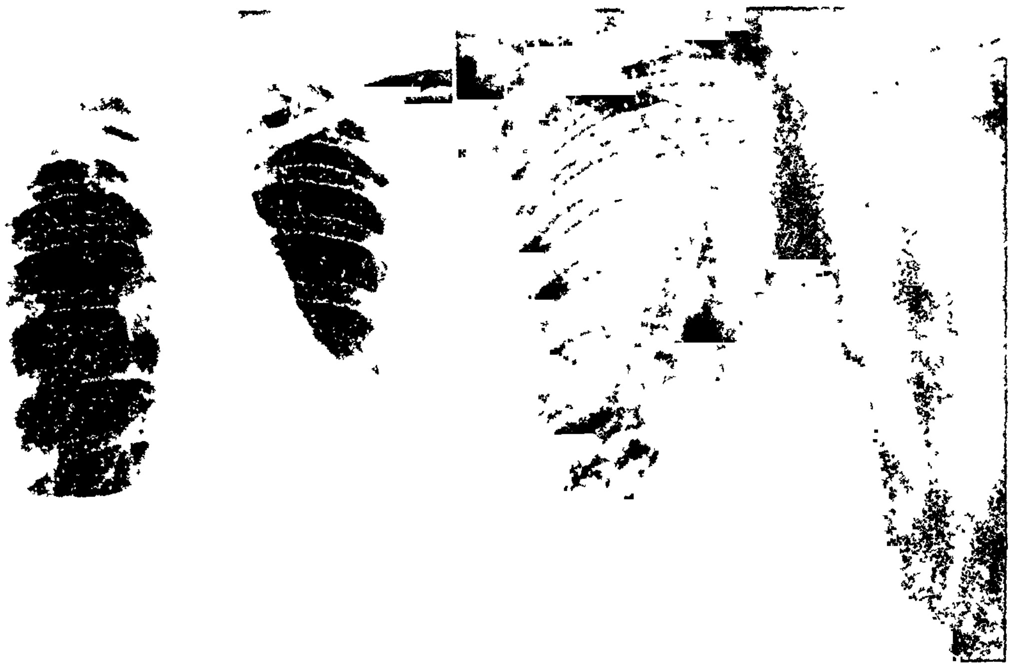


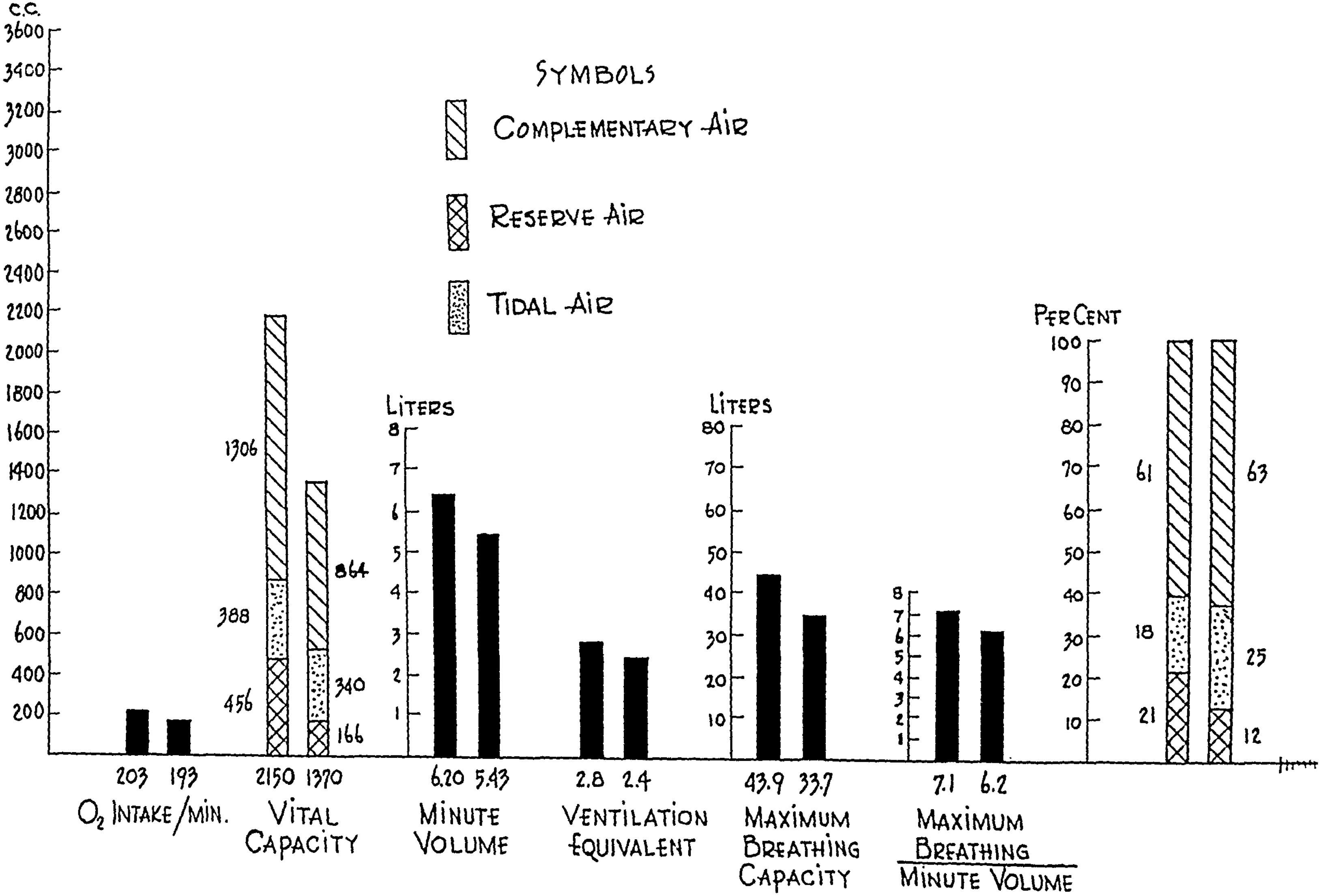
FIG 1 FIG 2

FIG 1 Chest X-ray film of patient E. G., March 28, 1941.

FIG 2. Chest X-ray film of same patient, November 3, 1941, four months after the third stage of a seven-rib thoracoplasty on the left.

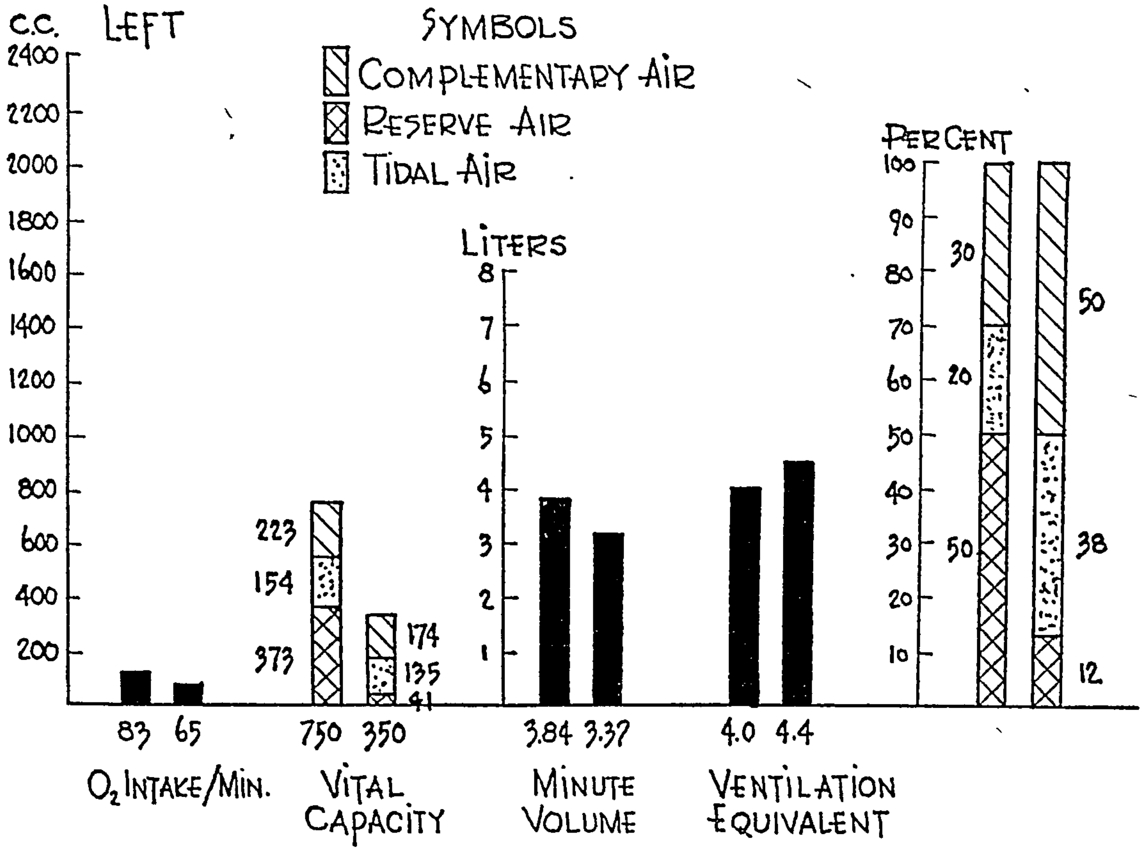
1937, apparently as technically unsatisfactory. Spirometry was done on March 15, 1941, bronchospirometry on March 24, 1941. The X-ray picture of March 28, 1941 (figure 1) shows: Left lung — involvement from apex to second anterior rib with fibrosis and multiple small cavities. Slight mediastinal shift to the left; costodiaphragmatic angle obliterated. Right lung — slight fibrosis from apex to second anterior interspace. A three-stage (seven-rib) thoracoplasty on the left was performed in March, May and July, 1941. The spirometric and broncospirometric studies were repeated on October 7, 1941 and October 10, 1941, respectively. The X-ray examination on November 3, 1941 (figure 2) showed: Upper seven-rib thoracoplasty on the left with moderate collapse. Slight scoliosis. Right lung unchanged; some deviation of the mediastinal structures to the right.

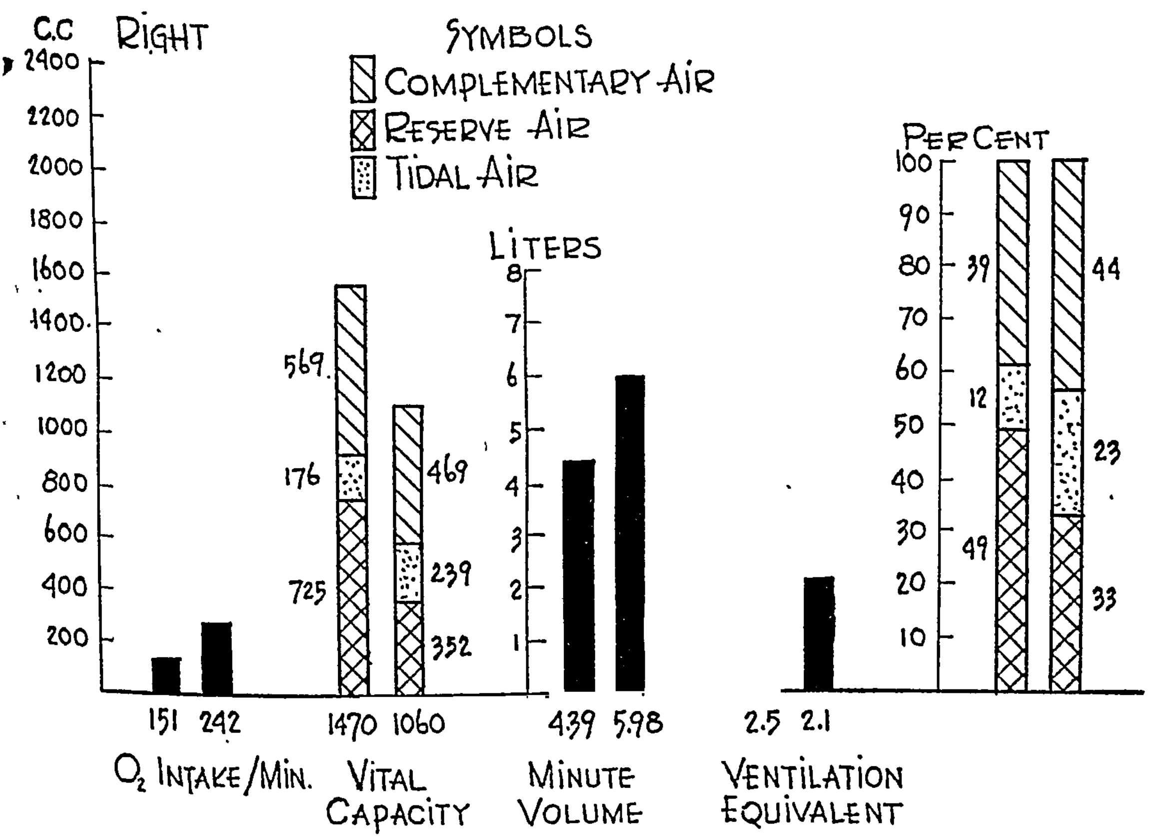
The spirometric findings were as follows (graph 1): (The first half of each double column presents the values before thoracoplasty, the second half, after thoracoplasty.) There



GRAPH 1. Spirometric findings in patient E. G.; the first half of each double column as of March 15, 1911 (before thoracoplasty), and the second half as of October 7, 1911 (after a seven-rib thoracoplasty on the left).

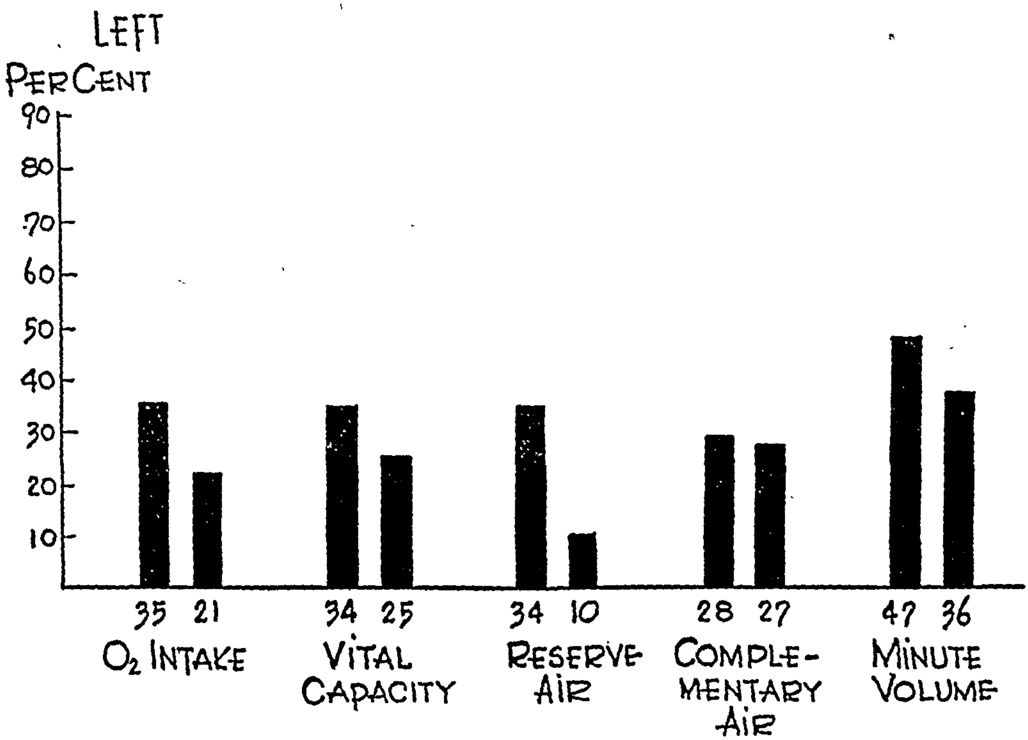
Note: In graphs 1, 2, and 3, the last two columns show the percentage distribution of the subdivisions of vital capacity before and after thoracoplas





GRAPHS 2 AND 3. Bronchospirometric findings in patient E. G.; the first half of each double column as of March 24, 1941, and the second half as of October 10, 1941.

was an insignificant decrease of the oxygen intake, associated with an insignificant reduction of the basal metabolic rate from −1 per cent to −3 per cent. Minute volume and tidal air decreased slightly, as did the ventilation equivalent. There was a considerable drop of the vital capacity and its subdivisions. The last pair of columns in graph 1 show that, in percentage of vital capacity, the tidal air increased from 18 to 25 per cent, the reserve air decreased from 21 to 12 per cent and the complementary air remained practically unchanged. Maximum breathing capacity and the factor $\frac{\text{Maximum breathing capacity}}{\text{Minute volume}}$, which were definitely below normal before the operation, showed only a moderate decrease.



GRAPH 4. Bronchospirometric data for left lung in per cent of total pulmonary function, before and after thoracoplasty.

Graph 2 reveals the changes which took place on the thoracoplasty (left) side; graph 3 those of the contralateral (right) side.

There was a slight decrease of the oxygen intake and the minute volume on the left side, a compensatory increase on the contralateral side. The ventilation equivalent on the thoracoplasty side had been high before the operation and remained high. The vital capacity dropped considerably on both sides. The decrease on the contralateral side is apparently caused by mediastinal shift and by the postoperative scoliosis, producing a narrowing of the interspaces in the upper portion of the right hemithorax.

Graph 4 shows the percentage that the left (thoracoplasty) lung contributes to the

total pulmonary function, before and after thoracoplasty. A normal left lung contributes approximately 46 per cent to the total pulmonary function and total pulmonary volume, respectively. Before the operation, this patient already had diminished functions of the left lung (with exception of the minute volume), caused by parenchymal disease, pleural obliteration and incomplete reëxpansion following pneumothorax, the figures ranging between 28 per cent for complementary air and 35 per cent for oxygen intake. Following thoracoplasty there was a further diminution of all figures.

DISCUSSION

Spirometric and bronchospirometric studies were done in 26 patients before and several months after four to eight-rib thoracoplasties.

There was only a very slight decrease of the oxygen intake and of the basal metabolic rate, definitely less than under pneumothorax treatment (Leiner (14)). Minute volume and tidal air, which did not change under pneumothorax treatment, showed either a slight increase or a slight decrease. The ventilation equivalent increased very slightly as it did in the pneumothorax group.

The average ventilation equivalent before thoracoplasty was slightly higher than before pneumothorax, apparently indicating that the thoracoplasty group as a whole had a somewhat poorer pulmonary function than the pneumothorax group. The originally poorer function in the thoracoplasty group is also seen in the factor $\frac{\text{Maximum breathing capacity}}{\text{Minute volume}}$, which is here definitely lower than in the pneumothorax group.

In 7 out of 25 cases the ventilation equivalent decreased, compared with 2 among 18 pneumothorax cases; apparently, thoracoplasty tends more often to improve the respiratory efficiency than pneumothorax because it is more successful in establishing selective collapse of diseased lung tissue.

The average reduction of the vital capacity was less pronounced than under pneumothorax treatment: 22 as compared with 30 per cent. Similarly, reserve air and complementary air decreased less under thoracoplasty than under pneumothorax. Therefore, the relative increase of tidal air in percentage of vital capacity was less under thoracoplasty than under pneumothorax.

The decrease of maximum breathing capacity and $\frac{\text{Maximum breathing capacity}}{\text{Minute volume}}$ was less extensive in the thoracoplasty cases than in the pneumothorax cases. In only 12 of 26 thoracoplasty cases was there a decrease of the factor $\frac{\text{Maximum breathing capacity}}{\text{Minute volume}}$, compared with 13 out of 18 pneumothorax cases.

On bronchospirometry there was a decrease of all data in the collapsed lung. However, the decrease of the oxygen intake was only about two-thirds of that under pneumothorax treatment. The oxygen intake decreased only 9 out of 17 times compared to 13 out of 17 times under pneumothorax.

The difference in the behavior of the ventilation equivalent between thoracoplasty and pneumothorax is striking. The decrease in the first, the increase in the last prove the better functional results of thoracoplasty.

Vital capacity, reserve air and complementary air dropped considerably, though definitely less than under pneumothorax treatment. The relative changes of the subdivisions of the vital capacity were less pronounced after thoracoplasty than under pneumothorax.

On the contralateral side the changes were less frequent and in average less extensive than in the pneumothorax cases. The compensatory changes were less obvious. The relation of the subdivisions of the vital capacity was hardly disturbed as compared with pneumothorax cases, possibly due to more rigid mediastinal structures and lesser increases in intrapleural pressures in the operated hemithorax.

The group of thoracoplasty patients is, of course, too small, and there are too great individual variations, each case showing different preliminary conditions, to permit final conclusions. Only some data showed a relation to the extent of the thoracoplasty.

The observation that thoracoplasty seems to affect pulmonary functions less than pneumothorax may be due to the following facts: (*1*) under thoracoplasty the collapse is more often "selective" than under pneumothorax; (*2*) the lung is more often more damaged prior to the operation than the lung which undergoes pneumothorax treatment; (*3*) a certain amount of restitution probably takes place in the thoracoplasty lung.

It is of course not entirely justified to compare the functions of thoracoplasty lungs with those of pneumothorax lungs; they should be compared with lungs reëxpanded after pneumothorax treatment. However, it has been pointed out in a previous paper (13) that such lungs frequently show very poor functions. More detailed studies of the function of reëxpanded pneumothorax lungs will soon be published.

SUMMARY

1. Pulmonary function was studied by spirometry and bronchospirometry in 26 patients before and after four to eight-rib thoracoplasties.

2. Total pulmonary functions showed in the average the following behavior: There was a slight, insignificant decrease of oxygen intake and basal metabolic rate. There was a slight increase of the minute volume of respiration and of the respiratory rate and a slight decrease of the tidal air. The ventilation equivalent increased slightly. Vital capacity, reserve air, complementary air, maximum breathing capacity and $\frac{\text{Maximum breathing capacity}}{\text{Minute volume}}$ showed a definite decrease.

3. Bronchospirometry revealed the following changes in the collapsed lung: a decrease of oxygen intake, minute volume and tidal air; a slight decrease of the ventilation equivalent, showing a more efficient use of the ventilated air. Vital capacity, reserve air and complementary air dropped considerably.

4. The contralateral lung was affected as follows: there was a compensatory

increase of the oxygen intake, a slight increase of the minute volume; tidal air and ventilation equivalent showed no significant change; vital capacity, reserve air and complementary air dropped slightly.

5. On the thoracoplasty side, the tidal air presented a larger part of the vital capacity after thoracoplasty than before. On the contralateral side, the relation of vital capacity to its subdivisions remained unchanged.

6. The impairment of pulmonary functions under thoracoplasty treatment is less severe than under pneumothorax treatment.

7. The results are illustrated by a representative case.

SUMARIO

1. En 26 enfermos se estudió la función pulmonar por medio de la espirometría y la broncoespirometría antes y después de ejecutar toracoplastias que comprendieron de 4 a 8 costillas.

2. Las funciones pulmonares totales revelaron en conjunto el siguiente comportamiento: hubo una leve e insignificante disminución de la entrada de oxígeno y del coeficiente del metabolismo basal, leve aumento del volumen respiratorio por minuto y de la velocidad respiratoria y leve disminución del aire inspirado y espirado. El equivalente de ventilación aumentó ligeramente. La capacidad pulmonar, el aire de reserva, el aire complementario, la capacidad respiratoria máxima y la $\frac{\text{capacidad respiratoria máxima}}{\text{volumen por minuto}}$ revelaron una disminución bien definida.

3. La broncoespirometría reveló las siguientes alteraciones en el pulmón aplastado: disminución de la entrada de oxígeno, del volumen por minuto y del aire entrado y salido; ligera disminución del equivalente de ventilación, revelando empleo más eficaz del aire ventilado. Descendieron considerablemente la capacidad pulmonar, el aire de reserva y el aire complementario.

4. El pulmón contralateral se afectó en la forma siguiente: hubo aumento compensador de la entrada de oxígeno, leve aumento del volumen por minuto; la corriente de aire y el equivalente de ventilación no revelaron alteraciones significativas; la capacidad pulmonar, el aire de reserva y el aire complementario disminuyeron ligeramente.

5. En el lado de la toracoplastia el aire inhalado y exhalado representó una proporción mayor de la capacidad vital despues de la toracoplastia que antes. En el lado contralateral no se alteró la reacción de la capacidad vital con sus subdivisiones.

6. La disminución de las funciones pulmonares es menos intensa con la toracoplastia que con el neumotórax.

7. Demuéstrase el resultado con un caso típico.

REFERENCES

(1) McIntosh, C. A.: Respiratory Physiology in Thoracic Surgery, Ann. Surg., 1935, *102*, 961.

(2) Lindskog, S. E., and Friedman, T.: The effect of thoracoplasty and phrenic paralysis on the total volume of the lung and its component parts, Am. Rev. Tuberc., 1936, *34*, 505.

(3) PINNER, M.: Physiological principles of collapse therapy, in Alexander's The Collapse Therapy of Pulmonary Tuberculosis, Charles C. Thomas, Springfield, Ill.
(4) KALTREIDER, N. L., FRAY, W. W., AND PHILIPPS, E. W.: Effect of thoracoplasty on pathologic physiology of respiration, J. Thoracic Surg., 1938, *7*, 262.
(5) HARTER, J. S., OVERHOLT, R. H., AND PERKIN, H. J.: The lung volume after thoracoplasty, J. Thoracic Surg., 1938, *7*, 290.
(6) LAMBERT, ADRIAN VAN S., BERRY, F. B., COURNAND, A., AND RICHARDS, D. W.: Pulmonary and circulatory function before and after thoracoplasty, J. Thoracic Surg., 1938, *7*, 302.
(7) SCHMIDT, W., AND GAUBATZ, E.: Spirometrische Funktions pruefung von Herz und Kreislauf, in Schmidt's Kollapstherapie der Lungentuberkulose, Georg Thieme Verlag, Leipzig, 1938.
(8) COURNAND, A., AND RICHARDS, D. W.: Pulmonary insufficiency: The effects of various types of collapse therapy upon cardiopulmonary function, Am. Rev. Tuberc., 1941, *44*, 123.
(9) BJÖRKMAN, S.: Bronchospirometrie. Eine klinische Methode, die Funktion der menschlichen Lunge getrennt und gleichzeitig zu untersuchen, Acta med. Scandinav., Supplem. 56, 1934.
(10) JACOBAEUS, A. C.: Bronchospirometry, J. Thoracic Surg., 1938, *7*, 235.
(11) LEINER, G., PINNER, M., AND ZAVOD, W. A.: Bronchospirography: 2. Application to collapse therapy: Preliminary report, J. Thoracic Surg., 1940, *10*, 32.
(12) VACCAREZZA, R. F., LANARI, A., BENCE, A. E., AND LABOURT, F.: Examen funcional de cada pulmón por separado en tisiologia, An. Cáted, de pat. y clin. tuberc., June, 1941, *3*, 5.
(13) PINNER, M., LEINER, G., AND ZAVOD, W. A.: Bronchospirography: II. The functional capacity of normal lungs, severely damaged lungs, lungs with strictly parenchymal lesions, thoracoplasty lungs, and re-expanded pneumothorax lungs, J. Thoracic Surg., 1942, *11*, 241.
(14) LEINER, G. C.: Spirometric and bronchospirometric studies in pneumothorax, Am. Rev. Tuberc., 1944, *50*, 267.
(15) LEINER, G. C.: Basal metabolism in pulmonary tuberculosis, Am. Rev. Tuberc., 1944, *50*, 223.
(16) WARRING, F. C.: Ventilatory function, Am. Rev. Tuberc., 1945, *51*, 432.

SPREAD OF TUBERCULOSIS IN FAMILIES OF TUBERCULOUS PATIENTS

P. K. TELFORD[1] AND RUTH GARTEN-WHITE[1]

A tabulation of the family records of patients with active tuberculosis under the supervision of the Los Angeles County Health Department has brought to light some interesting facts regarding the susceptibility of the members of certain families to the spread of this disease. Because any person may acquire tuberculosis, we have been inclined to discount the lay conception that there is a familial susceptibility or resistance to tuberculosis; but our figures have forced the conclusion upon us that there is some factual evidence in support of this belief. Some supposedly well-established factors in resistance and susceptibility must be reëvaluated with the accumulation of further data. We may consider these factors as falling into groups of slight, moderate and major importance: fresh air, sunshine, diet, occupation, physical and emotional strain, and so on down a long list.

Our figures show that a comparatively small proportion of the families exposed present nearly all of the new cases. The attributes of these families which make them more than ordinarily susceptible deserve earnest study. Preventive measures within or concerning the family will be successful in proportion as they are pointed toward the major elements of spread, and these are still not yet quite clear. A family is a complex unit, exhibiting characteristics, traits and habits representing the molding forces that have been in operation for generations. Even though the faults of these families may not be easily corrected, if they can be defined so as to be readily recognized, they can be made the object of intensive health supervision. These families merit a larger proportion of the tuberculosis prevention budget than is generally allotted to them, and more cases will be prevented by this means than by spreading available funds more thinly over the whole community.

Recent literature gives this problem some consideration. Rich (1) states: "In the case of tuberculosis, the influence of heredity is now regarded as a very real and a very important one, but it is regarded by most thoughtful students of the disease as a problem that still requires careful study before we shall be able to define its limits."

Puffer (2) quotes Hirsch, who stated in 1883 that disease occurs after contact but there is also another factor. He pointed out that consorts not related by blood, as well as relatives by blood, are included in the susceptible family groups. Thus he emphasized that transmission of infection is more likely to occur under certain conditions than under others.

Puffer also quotes from the Williamson County, Tennessee, studies showing that consorts to a spouse with a positive sputum and having tuberculosis in their family history have three times the number of manifest cases developing as those

[1] Los Angeles County Health Department, Los Angeles, California.

in the same status except with a negative past family history. She states that this evidence of familial susceptibility is a factor in the development of this disease, as well as is exposure to infection. She realizes, however, that massive exposure in childhood may have been a contributing factor in causing this difference.

Pottenger (3) has emphasized the occurrence of endogenous spread. The importance of possible early infection must be taken into account in considering the much greater extent of disease in consorts with a family history of tuberculosis as compared with those without such history.

Again Puffer quotes Pinner (4): "In the explanation of these changes, the relative frequency of susceptible and resistant strains is one prominent factor. The dying-out of susceptible strains leaves more favorable balance between susceptible and resistant strains which accounts in a large measure for the most prominent features of the epidemiological development." She makes much of this hopeful fact in her summary.

This thought makes it seem possible that Mendelian difference in hereditary familial resistance might explain the great resistance which is oddly exhibited by some siblings. This is possible although we "... are unable to explain the observed facts in human tuberculosis in terms of Mendelian theory." (Rich (1) p. 157.)

It is characteristic of tuberculosis in Southern California to be concentrated in a few restricted neighborhoods. The new cases, the location of which we visualize by the use of pin maps, reveal closely grouped cases in certain comparatively congested areas. These areas are inhabited chiefly by families in the low income brackets, with all the other attending conditions which favor the spread of disease. The cases in these areas are usually the newly diagnosed ones, in distinction to the groups of chronic cases of the foothill areas, new in residence only, the patients usually being those who have long known that they have tuberculosis and have moved to the foothills to obtain the benefit of the moderate altitude and the dry climate. It is toward the poor people in the congested neighborhoods that we have long directed our concentrated efforts in the prevention of the spread of tuberculosis.

Tuberculosis attack rates must be given careful consideration in choosing groups for survey work and for the application of other special preventive measures. The slogan "An X-ray of Everyone" points to an ideal goal, performs useful groundwork and aids physicians in thinly populated areas, but should not deter large health agencies from carefully planning the use of the bulk of available funds on selected groups. Local surveys made in our congested neighborhoods have been a full-time activity of our departmental survey group for the past four years. A house-to-house canvass in poor neighborhoods has detected five times as much active pulmonary tuberculosis as has been found by an equivalent amount of effort expended in other types of surveys. One must acknowledge the fertile field found in public institutions as emphasized by Edwards (5) and others, but that is quite unrelated to our present study. We desire more information about the reasons for spread in the homes where tuberculosis thrives. We work

in the homes, thus examining not only the wage-earner but all other adults and the older children.

Crowded living quarters constitute a major fault. It has been felt by some that this is primarily an economic problem. But in spite of generally improved economic conditions, we should not lightly dismiss this factor as one that no longer plays a major rôle. Thousands of these families have been moved to modern housing projects and many of them have been earning big wages for years, but too often they have reverted to their old living habits *within* the new multifamily dwellings. These habits had been gradually molded into inherent characteristics that will require long and painstaking efforts to change. The more intimately we know them, the more effectively can we work to improve them.

In 1940, the clinicians in the Tuberculosis Division of the Los Angeles County Health Department analyzed the family records of all our cases of active reinfection type tuberculosis to determine the effects of contagion in the family. The distant past history of the families was ignored and only those conditions tabulated which occurred during the life of our records. All cases found in the family within six months of the time the first case in the family was diagnosed in our clinic were considered as original cases. Only those detected thereafter were considered as new cases whose infection was presumably due to exposure during the period the family was under observation. Likewise, contacts with no active tuberculosis were not included in our tabulations unless they had been under observation six months or longer.[2]

Table 1 shows the figures for 506 families with 595 original cases and 1,637 other persons exposed. There were 135 new active cases developing among these exposed persons, or 8.25 per cent. Of these, 4 were active nonpulmonary, 45 were active primary and 86 active reinfection type pulmonary tuberculosis. In other words, slightly more than 5 per cent of the 1,637 contacts developed active reinfection type pulmonary tuberculosis six months or more after the discovery of the first known case in each of the respective families.

In table 1 the families were divided into four groups with different degrees of exposure. In the group with but one active original case, and it having a negative sputum, the amount of spread was less than one-half that in any of the other groups. However, there is evidence of a real danger to contacts even in this group.

We have here data bearing on the attack rate in the families of tuberculous patients, which is much more important than that for the whole population. The results further emphasize the need for a meticulously complete control of known cases and supervision of all family contacts as the first steps in prevention and case-finding, even though the known cases do not have positive sputum.

[2] Although this is a convenient segregation, it is a bit faulty. It assumes that all members of the family were examined within six months of the discovery of the first known active case in the family, and that all examinations after six months were reëxaminations, which is not entirely true; but we know from the type of supervision we practice that exceptions are rare and consist largely of contact examinations enforced by legal order or some delayed for other reasons.

Table 2 shows the length of exposure in months and length of observation thereafter of persons in table 1.

Table 2 divides the contacts in the same family categories as shown in table 1 and shows for them both the average length of known exposure in months and

TABLE 1

1940 Study

	NUMBER	ORIGINAL CASES	CONTACTS	NEW CASES		NO ACTIVE DISEASE	
				Number	Per cent	Number	Per cent
Families with a positive-sputum case and more than one active original case	36	90	116	15	13.0	101	87.0
Families with a positive-sputum case and no other active case within six months	236	236	774	78	10.0	696	90.0
Families with more than one original case with negative sputums	25	60	92	13	14.0	79	86.0
Families with a negative sputum case and no other active case within six months	209	209	655	29	4.5	626	95.5
Totals	506	595	1,637	135		1,502	

TABLE 2

1940 Study (continued)

NEW CASES			CONTACTS DEVELOPING NO ACTIVE DISEASE		
Number	Average months of exposure per case	Average months of observation per case, while not exposed	Number	Average months of exposure per individual	Average months of observation per individual after termination of exposure
Families with a positive-sputum case and more than one active original case					
15	15	32	101	16	17
Families with a positive-sputum case and no other active case within six months					
78	19	18	696	32	16
Families with more than one original case with negative sputum					
13	31	15	79	31	15
Families with a negative-sputum case and no other active case within six months					
29	25	10	626	24	9
135			1,502		

the average length of clinical observation while not exposed on account of the removal of the case or cases from the home, if such separation was accomplished. These contacts are divided into two groups: the first includes those that developed active tuberculosis; the second group those who did not.

Data in tables 1 and 2 cover our experience during the latter half of the 1931–1940 decade. They depict conditions during the worst years of the depression. Now, four years later, the staff has analyzed all of the present active cases as far as practicable, eliminating the families tabulated in the previous report. Unquestionably, there was improvement in the economic status of these families in the period covered in this latest report. There was less cause for congestion within the home, and with better living conditions and improved nutrition there should have been less likelihood of the spread of infection. The average number of months of exposure of contacts was also much less, because of improvement and extension of our isolation technique. A prediction of a definitely lower attack rate based on these premises might, therefore, seem justifiable, but the results show that such a prediction would be in error. In 431 families with 1,264 contacts, 60 cases of active reinfection type pulmonary tuberculosis developed

TABLE 3

	FAMILIES	PERSONS	ORIGINAL CASES OF TUBERCULOSIS	CONTACTS PER FAMILY	CONTACTS NOT DEVELOPING DISEASE	CONTACTS DEVELOPING DISEASE
No contacts	33	33	33	0	0	0
No new cases	350	1,395	361	3.0	1,034	0
One new case	40	212	40	4.3	132	40
Two new cases	5	39	5	6.8	24	10
Three new cases	2	17	2	7.5	9	6
Four new cases	1	10	1	9.0	5	4
	431	1,706	442		1,204	60

among the contacts, or an attack rate of 4.75 per cent. This is very little lower than the rate found in our previous survey.

The great hazard in these families with this high attack rate is apparently not only due to the direct spread of the infection which we as health officers constantly emphasize, but to many other conditions favoring the spread. As has been suggested by others, there must be some inherent fault either in their physical or their mental make-up which makes the members of these families more susceptible than the average person; or there may be contributory domestic habits that have not been overcome by the usual public health education and supervision.

Conditions in other families in similar communities were found to be quite different. The house-to-house X-ray surveys previously mentioned were carried on in the most congested parts of these same areas, and 22,000 persons examined showed an attack rate of 0.5 per cent.[3]

[3] Statistics of tuberculosis diagnosis by X-ray surveys are usually not comparable to clinic figures and, because of differences in technique and criteria for cases, they are seldom comparable with each other. Cases in each instance here tabulated constitute diagnoses of active disease by clinic study.

The greater tendency to spread in certain families, in comparison with other families, is demonstrated by the fact that in families having more than one case, even where no positive sputum can be found, there is a high attack rate. In other words, while there may be only intermittent and rare periods when a positive-sputum condition exists in the home with more than one case, yet there is apparently a marked tendency in these homes for infection to spread to others.

Table 3 summarizes the results of the recent review. In this table we have divided the cases into six divisions: First, those who had no contact, single persons; second, those families in which there were contacts and no new cases developed; third, those families with contacts and one new case developing; fourth, those families with contacts and 2 new cases developing; fifth, those families with contacts and 3 new cases developing; sixth, those families with contacts and 4 new cases developing. The definition of original cases and new

TABLE 4

Diagnoses:		
Minimal	70 cases, or 16 per cent	
Moderately advanced	166 cases, or 39 per cent	
Far advanced	195 cases, or 45 per cent	
	431 cases	100

TABLE 5

Positive for acid-fast bacilli	293 cases, or 68 per cent
Negative for acid-fast bacilli	130 cases, or 30 per cent
Sputum not examined by us	8 cases, or 2 per cent

cases is the same as for table 1, as explained above. It is a remarkable fact that, in the 431 families reviewed, there were only 48 families in which one or more new cases developed, but this fact is partly explained by the larger number of contacts per case in these families.

The status of the disease in the group of patients consisting of the first case discovered in each of the 431 families is shown in table 4.

This agrees fairly well with the epidemiological report by the California State Department of Public Health for the year 1943 (6), their figures being: minimal, 21.2 per cent; moderately advanced, 33.7 per cent; far advanced, 43.6 per cent.

The sputum analyses for the group of patients consisting of the first case discovered in each of the 431 families are shown in table 5.

The cases with sputum not examined by us were emergency cases. They were sent to the hospital and the laboratory work was completed there.

We have always thought of the communicability of tuberculosis as a problem within the home where there was prolonged exposure to a positive-sputum case and a lowered resistance. Let us see if this holds true in the 48 families who were the offenders in this survey group. These 48 families gave rise to the 60 new

cases of tuberculosis, making the attack rate in the 1,706 contacts of all of the families 4.75 per cent. If these 48 families are considered separately, their 278 contacts had an attack rate of over 21 per cent. Their exposure while under clinic supervision is shown in table 6.

The sputum analyses for the 48 original cases in these families are shown in table 7.

There is a question as to the sputum analysis of this last case. The type of specimen examined may have been unsatisfactory and a sufficient number of

TABLE 6

FAMILIES	AVERAGE EXPOSURE
40—One new case to the family	17 months
5—Two new cases to a family	15 months
2—Three new cases to a family	14 months
1—Four new cases to a family	30 months

TABLE 7

	ORIGINAL CASE WITH POSITIVE SPUTUM	ORIGINAL CASE WITH NEGATIVE SPUTUM
40—One new case to family	31— 77.5 per cent	9— 22.5 per cent
5—Two new cases to family	3— 60.0 per cent	2— 40.0 per cent
2—Three new cases to family	2—100.0 per cent	0— 0 per cent
1—Four cases	0— 0 per cent	1—100.0 per cent

TABLE 8

A. Patient potentially able to buy supplemental medical care (*e.g.* roentgenogram, drugs and supplies)	67 cases, or 20 per cent
E. Patient unable to buy supplemental medical care	210 cases, or 62 per cent
R. Recipient of relief and therefore unable to buy supplemental medical care	60 cases, or 17 per cent
? No social history taken	3 cases, or 1 per cent
	340 cases, 100 per cent

specimens may not have been run. If we accept the report, however, the average in the four groups shows a positive sputum in 75 per cent of the original cases. An average of the first three groups shows 77 per cent of the original cases having positive sputum.

A new division was made in this survey. Ignoring for the moment the families developing active primary tuberculosis and no other type, the economic status was tabulated for those families developing active reinfection type pulmonary tuberculosis in the contacts, and is shown in table 8.

This division into economic status seems important. We have always thought that the economic level played a rôle in tuberculosis. Poverty and social maladjustment were often present in these homes; only 20 per cent were able to pay for medical care. There is nothing about poverty which by itself lessens resistance, but poverty often does set up conditions which give the tubercle bacillus a chance to spread.

Yet the economic status was not a prime factor. In the group of families with 2 new active cases developing six months or more after the original case was discovered, we found 5 families, or 60 per cent of this group, able to afford private medical care. All 5 of these families were in one area and belonged to the same social group. It has been suggested that perhaps these families had not lived long enough under the improved standard of living that we have had the last four years. It may take added years on a higher economic standard before the resistance of these families is improved. Confirming the family element in their susceptibility is their comparatively shorter exposure. Eighty per cent of the original cases in this group were diagnosed as having minimal tuberculosis and only 40 per cent had a positive sputum, in contrast to the whole number of families studied, in which the figures were 16 per cent minimal and 54 per cent positive sputum.

With this high attack rate in certain groups of families, it would seem justifiable to isolate out of the home every active case occurring in families with histories of considerable tuberculosis. That seems to be the best conclusion, although we have demonstrated in two separate projects that the same object may be attained either in this way or in another, which, however, is often too difficult to attain. The effectiveness of isolation of every active case out of the home was shown in a neighborhood in the Clearwater district, where 9 deaths occurred in eighteen months in a small group of houses. An arbitrary edict was issued that no active case would be permitted to remain at home in that neighborhood, regardless of other circumstances. This stopped the spread and, except for rare importations, there have been no new cases. The other demonstration was in the San Antonio district, where there were a number of ex-sanatorium, chronic, advanced, communicable cases that it was found possible to isolate within the homes with a little extra material assistance and under intensive supervision, with at least daily visits by some worker from our Department. This procedure was found to be effective in stopping the spread of infection, and we considered the cost less than institutional care, but we were unable to have it officially adopted by other districts on account of various insuperable obstacles.

We can conclude, at least, that isolation is essential in this type of family, preferably out of the home, or else in the home with considerable material assistance and intensive supervision. If this were done, wouldn't our attack rate be less and wouldn't we have fewer cases of tuberculosis due to familial contacts?

SUMMARY

1. A review was made of families with active pulmonary tuberculosis and their familial contacts. Two surveys were made four years apart.

2. The attack rate among contacts was 5 per cent and 4.75 per cent, respectively, in the two different periods.

3. The economic status was improved during the period of the last survey, but did not influence the findings to any appreciable extent.

4. Isolation of active cases of tuberculosis, either outside the home or in the home with intensive supervision, should be stressed in proportion to the number of cases in the family or to cases known in recent family history.

SUMARIO

1. En un estudio de ciertas familias con tuberculosis pulmonar activa y de los convivientes familiares realizáronse dos pesquisas a plazos de cuatro años.

2. El coeficiente de ataque entre los convivientes representó 5% y 4.75%, respectivamente, en las dos ocasiones.

3. El estado económico mejoró durante el período del último estudio, pero no afectó mayor cosa los hallazgos.

4. Debe recalcarse el aislamiento, bien fuera del hogar o en el hogar con vigilancia intensa, de los casos activos de tuberculosis, en proporción al número de casos en la familia o de casos que revele la historia familiar reciente.

REFERENCES

(1) Rich, A. R.: The Pathogenesis of Tuberculosis, Charles C. Thomas, 1944.
(2) Puffer, R. R.: Familial Susceptibility to Tuberculosis, Harvard University Press, 1944.
(3) Pottenger, F. M.: Am. Rev. Tuberc., 1944, *50*, 112.
(4) Pinner, M.: Am. Rev. Tuberc. 1940, *42*, 382.
(5) Edwards, H. R.: Am. Rev. Tuberc. 1943, *47*, 308.
(6) California's Health, Vol. 1, No. 14, January 31, 1944.

COMMUNITY ORGANIZATION FOR MASS CHEST X-RAY SURVEYS

A Plan in Operation in Delaware County, Pennsylvania[1]

J. W. CUTLER,[2] A. M. SHARPE,[3] J. W. WOOD[3] AND R. W. BERNHARDT[3]

It is universally recognized that tuberculosis is almost symptomless at its onset and may go undetected for a long time until it has reached an advanced stage, not infrequently until after the disease has been communicated to others. Since the patient will not seek the physician during the early stages of the disease, because he is not aware that anything is wrong, the physician must find ways and means to seek him.

Experience has shown that the only entirely satisfactory method of finding undiagnosed cases of pulmonary tuberculosis consists in making X-ray films of the chest of every person in the community, studying in detail those with abnormal findings and repeating the process at regular intervals (1).

To conduct mass X-ray surveys in the community and yet preserve standards of medical ethics, build harmony between the practicing medical profession, the departments of health and the voluntary associations, and at the same time stimulate a maximum of initiative and active participation on the part of the public, presents a pressing problem in organization and coöperation.

Can the departments of health and voluntary associations expect to get the majority of practicing doctors actively and continuously interested in coöperating in tuberculosis case-finding? This question takes on immediate importance with the recent creation of a Federal Tuberculosis Control Division authorized by Congress to spend at least $10,000,000 annually for the prevention and control of tuberculosis (2).

There have been many instances, particularly since the outbreak of the war, when private and public agencies have united in local communities to accomplish the mass chest X-raying of industrial workers. Cleveland, Philadelphia and Portland are only a few of the places where it has been done (3).

The well known Detroit Plan, under the leadership of Doctors Vaughan and Douglas of the Detroit City Department of Health, is also a notably successful effort in the dual task of case-finding and of establishing harmonious medical relationship (4, 5).

TUBERCULOSIS CASE-FINDING IN DELAWARE COUNTY

This presentation concerns itself with the development of a coöperative community case-finding program in Delaware County, Pennsylvania, where the practicing medical profession has assumed active leadership.

The program embodies features which are established practices in many parts of the country and nothing distinctly new is claimed. The approach, however,

[1] Approved for publication by the Delaware County Medical Society, the Delaware County Tuberculosis and Health Association, and the Departments of Health.

[2] Philadelphia, Pennsylvania.

[3] Chester, Pennsylvania.

is from a somewhat different angle with greater emphasis on comprehensive community organization and on the more active part of the family physician and local specialist in case-finding. The plan is sufficiently novel we believe to warrant publication.

Conditions prior to 1943: Delaware County in Pennsylvania is typical of many counties throughout the United States. It had a pre-war population of 310,756 residents scattered over 185 square miles of territory, with no dense areas of population comparable to those found in large cities. Chester, its only city, had a 1940 population of 59,285. There are 25 boroughs in the county, 10 first-class ond 11 second-class townships. The density of population varies from 6,493 to the square mile in upper Darby Township, the most densely populated first-class township, to 422 in Aston Township, a strictly rural community.

The tuberculosis control program was not well coördinated. There was a State appointed District Medical Health Officer for the county, the local voluntary Tuberculosis Association, the Tuberculosis Committee of the County Medical Society, three State Tuberculosis Clinics and the local health and welfare agencies. Tuberculosis case-finding was carried on in the county from time to time by the voluntary Tuberculosis Association through a tuberculin testing program, and occasional X-ray surveys were done by the State, but only on a very small scale.

Prior to 1943 approximately 5,500 county residents (mostly high school students) were surveyed by all agencies concerned. This represented only 1.7 per cent of the population.

The practicing medical profession was not an active participant in these surveys. After negotiations between the physicians and the voluntary Association, X-ray films were made on tuberculin reactors by roentgenologists, on a small fee basis. The County Medical Society was opposed in principle to many of the practices followed. The local health departments, for the most part, were inactive. Such was the state of affairs in Delaware County prior to 1943.

Organization of the Delaware County Chest Survey Committee: Wartime changes in the county, especially in increased and shifting population, dictated the growing need for a more comprehensive and coördinated case-finding program; one which would be available to the entire population at periodic intervals, and which would rally around it all elements in the county. The solution was the formation of a Chest Survey Committee for Delaware County, which would represent all groups in the county interested in tuberculosis, and which would be the means through which plans for mass X-ray surveys in the county could be cleared, crystallized and clarified harmoniously and without duplication of effort.

The very first problem was to establish a working agreement between the local voluntary Association and the Delaware County Medical Society. Exploratory meetings between representatives of these two groups were begun in June, 1942. After twelve months of continued effort a final agreement approved by the Board of Directors of the County Medical Society and of the Delaware County Tuberculosis and Health Association was reached in June, 1943. Case-finding under the joint sponsorship of the two groups began soon thereafter. In the ensuing six months 3,989 county residents were surveyed. The cost of the surveys was defrayed by the voluntary Association. Of these surveys, 2,844 were made in schools and 1,145 in industry.

The experiment in coöperation was so successful that the voluntary Association included in its budget sufficient funds to survey 12,000 persons during the following fiscal year (April 1, 1944 to March 31, 1945), 11,487 of whom have already been surveyed at the time of this report. Discussions were begun with representatives of health departments, with labor, industry and the general public, in the endeavor to broaden the base of the County Chest Survey Committee and to create a strongly organized and smoothly coördinated community case-finding program for the entire county.

DELAWARE COUNTY CHEST SURVEY COMMITTEE

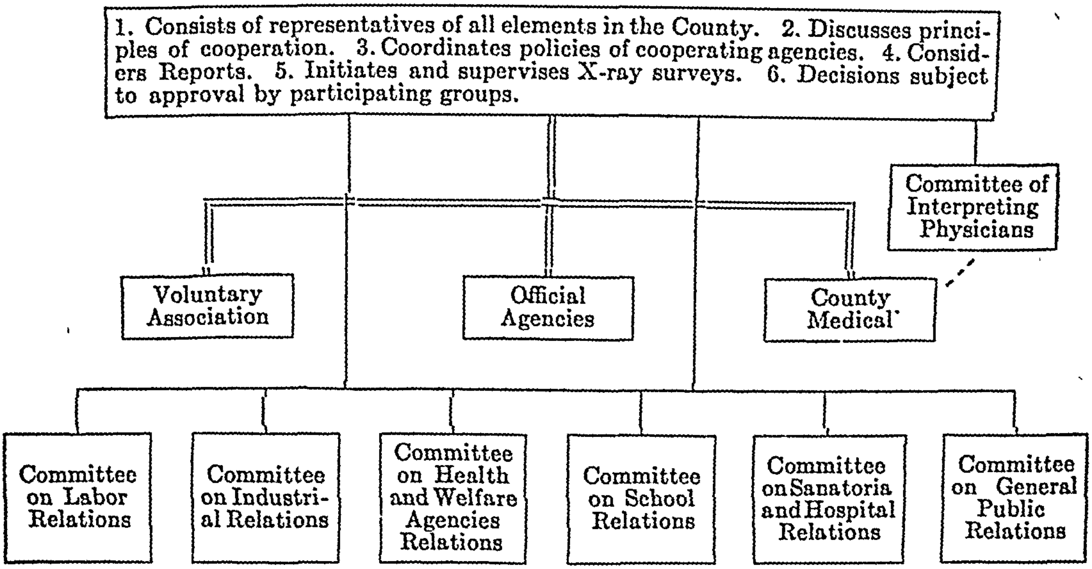


Chart of Relationships and Committees for Chest X-Ray Surveys

Chart 1. Every phase of the program has been worked out with a view of maintaining physician-patient relationship, of protecting the privacy of the individual examined, and of mobilizing and activating the latent determination of the public to eradicate tuberculosis from its ranks. It operates on the principle of local determination of need and local control of administration, but full coöperation with federal, state and local government projects.

As organized at the present (chart 1), the Chest Survey Committee of Delaware County consists of 12 members made up as follows: 2 representatives each from the County Medical Society, the voluntary Tuberculosis Association, the Departments of Health; and one each from the general public, labor, industry, schools, health and welfare agencies and hospitals and sanatoria. In some instances membership is interlocking, the same individual being a member of two or more groups, thus creating increased harmony. To further cement harmony the executive secretary of the Delaware County Tuberculosis and Health Association is also secretary of the Chest Survey Committee.

Future plans call for standing committees on Labor Relations, Industrial Relations, Health and Welfare Agencies Relations, School Relations, Sanatoria

and Hospital Relations, and finally General Public Relations. Each committee is to be composed of representatives from their respective groups. The chairman of each standing committee, in turn, is also to be a member of the Chest Survey Committee as the representative of the group.

These standing committees are planned to be made virtually independent bodies whose primary function will be to study the problems arising from tuberculosis case-finding as such problems may affect the respective elements of the population.

Not only are these standing committees expected to make recommendations to safeguard the interests of the different groups in the community, but also to take an active part in policy making, in supervising case-finding and in furthering the movement throughout the county. In essence, therefore, the standing committees are to be the counterparts of the Delaware County Medical Society and the Delaware County Tuberculosis and Health Association. In this way a democratic base will be founded for community interest in tuberculosis case-finding under local guidance and responsibility, and in a position to coöperate with federal, state, and local government projects.

PRINCIPLES OF COÖPERATION

With the basic idea of a Chest Survey Committee a reality, the next step was to formulate a code of principles and ethics. The following gives the fundamentals of the program as it now operates:

(*1*) *Chest Survey Committee:* Its main functions are to establish harmony of purpose, develop community coöperation, avoid duplication of effort and direct tuberculosis case-finding along progressive and scientific lines.

All major decisions of the committee, however, are subject to the approval of the County Medical Society, the County Tuberculosis Association and the Departments of Public Health, the three parties most vitally interested in tuberculosis case-finding in the county. On the other hand, in return for this veto power, the Health Departments, the County Medical Society and the voluntary Tuberculosis Association clear all their plans for tuberculosis case-finding in the county and, whenever possible, execute them through the Chest Survey Committee.

Decisions pertaining to labor and industry or other groups are approved by their respective committee on labor or industry or schools, as the case may be. The only power the Chest Survey Committee can have, consequently, is that delegated to it by the agencies that it represents. Thus are met the needs and interests of all groups.

(*2*) *Limitations of mass chest radiography:* The object of mass radiography is to pick out in a group of ostensibly healthy persons those persons with abnormal X-ray findings, who are in need of a full clinical examination (6, 7). A complete diagnosis and the decision concerning the necessity for hospitalization and treatment can be based only on the evaluation of many factors, such as history, clinical observation and sputum and sedimentation rate findings, as well as detailed X-ray studies. The report to the physician on the survey film must necessarily be brief, in keeping with this concept, and serve primarily as a lead.

(3) *Participation of family physician:* It is essential that the private physician under proper guidance, becomes the backbone of the case-finding movement, the central figure about whom the whole program revolves. His private office must be recognized as the logical subcentre of activity in the diagnosis, prevention and control of tuberculosis, as it relates to the individual patient and his family (8, 9, 10, 11, 12, 13).

The private physician commands the confidence of the public, and knows the health needs of his patients in that peculiarly intimate manner possible only to a physician. It is he who can best bring preventive measures most effectively to bear where they are most needed. It is he who can decentralize public health and humanize and individualize tuberculosis control. He is the logical person through whom can be executed the organized effort of the community in finding unsuspected tuberculosis. Mass X-ray case-finding, then, should be so conducted as to enhance his prestige and professional standing, and enable him to emerge as a strong champion of preventive medicine and as a wise counselor in matters pertaining to tuberculosis. This can be accomplished only with the fullest coöperation and understanding on the part of the official health departments and voluntary agencies.

With these thoughts in mind, and in order to strengthen physician-patient relationship, the name of the family physician, so designated by the person X-rayed at the time of the survey, is to become a part of the survey record, and X-ray reports of the findings are sent only to the specified family physician. Where there is no family physician the person X-rayed is asked to name a physician in his immediate neighborhood. Following the survey the patient with suspected disease is notified to seek medical advice and further study from his own family physician, to whom a report of the findings has been sent.

Follow-up is done in such a manner as to bring the person suspected of having tuberculosis in contact with his designated family doctor (chart 3). Once contact is established between family physician and patient, the physician is encouraged by the Chest Survey Committee to complete the diagnosis, evaluate the findings, suggest treatment and arrange for consultations with consultants of his own choosing; and when necessary, to give the patient a note of admission to a public chest clinic. (In case of clinically significant tuberculosis he should, of course, report the case to the local health department in compliance with the law.) Furthermore, the family physician is encouraged to make contact studies of other members of the household and to act as a clearing-house on all tuberculosis problems that relate to his patient and the family (chart 3).

The channeling of all activities relating to the patient and the family through the family physician is bound to be of tremendous educational value in keeping the general practitioner tuberculosis-minded and abreast of the latest techniques in the diagnosis and treatment of this disease. He in turn will help influence his patients to be intelligently informed about tuberculosis. Thus the cycle will be complete. The principle, therefore, of putting upon the private physician much of the responsibility of diagnosing tuberculosis in those of his patients in whom the disease is suspected is a logical step and is fundamental to the eradication of

this disease. It is also the surest way of overcoming the various questions of economics, medical ethics, relationship between the practicing medical profession, the voluntary Tuberculosis Association, official departments of health and other groups.

(4) *Participation of local roentgenologist and quality of X-ray reports:* A high standard of quality of X-ray reports to the family physician is a prime essential of good mass X-ray screening. Anything that would weaken public confidence in mass radiography would impair its usefulness. So also would anything that would lead the public to expect too much from this method. A correct interpretation of the survey film is accordingly paramount and the interpretation, of necessity, requires great radiographic skill. Only qualified roentgenologists, pthisiologists or experienced public health doctors possess this skill. All such physicians in the county comprise a Committee of Interpreting Physicians to interpret survey films, this being under the auspices of the Chest Survey Committee (chart 1).

The use of local talent to the greatest extent possible to interpret survey films encourages every qualified physician in the county to become an active participant in case-finding. This tends to widen responsibility and initiative, and affords those physicians invaluable experience in the early diagnosis of tuberculosis by X-ray, with resultant higher standards of local roentgenography.

This committee of experts studies the various technical phases resulting from X-ray surveys. It also agrees on types of reports sent to the family physician, decides on the qualifications of members to the Committee of Interpreting Physicians, determines questions of compensation for interpretation of films, and helps formulate conditions under which X-ray surveys are to be conducted. Too, the Committee meets in scientific sessions to exchange experiences and discuss problems arising from the interpretation of films, with the objective of constantly improving the quality and usefulness of the X-ray survey reports to the family physician.

The following types of reports and their diagnostic significance have been approved by the Committee of Interpreting Physicians, to be sent to the family physician:

(a) *Negative or normal:* One normal report should not be looked upon as final if there is the slightest clinical evidence to the contrary. If the family physician has reason to believe the report should be otherwise, he should not hesitate to conduct a more detailed investigation.

(b) *Healed primary tuberculosis:* The importance of this diagnosis from the public health standpoint is the warning to look for possible tuberculosis in other members of the household as the source of infection. It is among the contacts in this group that unsuspected tuberculosis is most likely to be found. All contacts should be X-rayed.

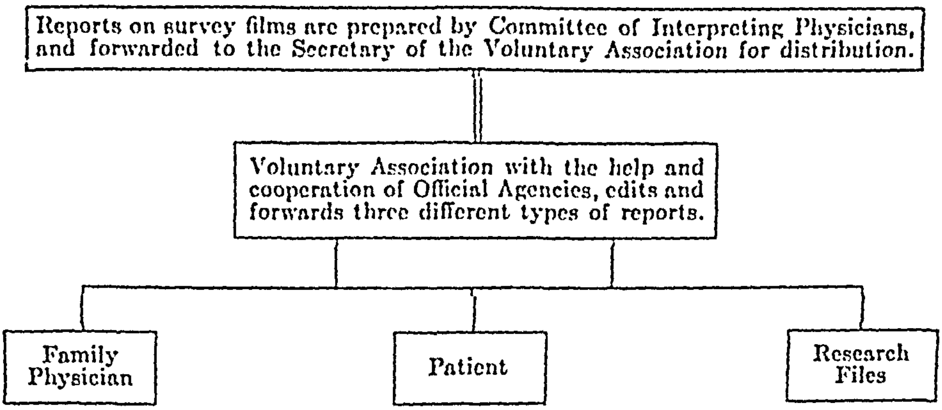
(c) *Questionable disease, further supervision and study indicated:* This diagnosis is based on abnormal findings in the X-ray film which cannot be clearly classified as pathological. Time alone can determine the clinical significance of the X-ray findings. If tubercle bacilli are present in the patient's sputum or gastric juice, modern treatment should be instituted promptly.

(d) *Significant findings, minimal disease, probably tuberculosis:* This patient is in need of a thorough clinical examination including sputum studies and detailed X-ray films. The disease may be well stabilized and require only periodic observation. Time alone can determine the clinical significance of the X-ray findings. If tubercle bacilli are present, modern treatment should be instituted promptly.

(e) *Significant findings, advanced disease, probably tuberculosis:* This patient is obviously in need of a thorough clinical investigation, including X-ray films, sputum examination, sedimentation rate and other studies. If signs of active disease or positive sputum are present, modern treatment should be begun promptly to save time and life, and to safeguard the contacts from continued infection.

(f) *Significant findings other than tuberculosis, supervision and study indicated:* This diagnosis is based on significant findings in the X-ray film other than tuberculosis. Further clinical investigation is indicated, including detailed X-ray studies.

REPORT ON SURVEY FILM



Physician receives one of six standardized reports for each patient surveyed, appropriate to the condition found (normal, disease suspected—supervision indicated, healed primary tuberculosis, minimal tuberculosis, advanced tuberculosis, disease other than tuberculosis).

Patient receives one of six standardized reports appropriate to the condition found, corresponding to the report mailed to the physician.

The original report from the Committee of Interpreting Physicians is kept in research files for future study.

CHART 2. An appeal from the County Medical Society to support the case-finding survey by promptly completing the diagnosis is included with reports to the family physician in all cases with questionable and significant findings.

These reports are to be mailed to the family physician in card form suitable for filing with his other records of the case. An appeal from the County Medical Society to support the case-finding survey by promptly completing the diagnosis is sent with reports of all questionable and significant findings. The original report by the interpreting physician, including a chest diagram of the findings, is retained for research (chart 2).

Reports to persons examined are of such nature as to create a desire to complete the diagnosis through private channels without producing fear or anxiety.

To safeguard against poor interpretation resulting from technically defective

films, or for any other reason, the physician reading survey films may order reexamination with conventional 14″ x 17″ celluloid films and delay his report until he has had an opportunity to study the new films. These latter films are conveniently referred to as "station films." Requests for station films are honored promptly at designated stations (hospitals and physicians' offices) throughout the county, at no cost to the person surveyed. The cost of the station film is met by the Delaware County Tuberculosis and Health Association. (The Association pays $3.00 for each station film.) Station films should be resorted to liberally in all doubtful cases.

The chairman of the Committee of Interpreting Physicians assigns the films for interpretation in rotation to the different doctors of the Committee, so that the number of cases per interpreter equalize themselves during the year.

A statement of reading is sent to each interpreting physician semi-annually, and reimbursement made at the same time. (The Tuberculosis Association covers the cost at the rate of 25 cents per reading. Should the volume of work warrant it, it is planned to have a paid part- or full-time qualified physician do most of the readings.) At the beginning of each fiscal year the Committee of Interpreting Physicians votes to read a liberal number of survey films without compensation, as a public service, to further the educational program of the Delaware County Tuberculosis and Health Association. During the past fiscal year 1,500 films were interpreted without compensation. At the end of each year each member of the Committee receives a report of the number of cases interpreted by the various members, together with a summary of the findings.

(5) *Follow-up of diagnosed cases:* The success of any chest survey program must be measured in terms of follow-up, of the number of newly discovered cases placed under observation and treatment. All the resources of the community, therefore, are coördinated in the one common effort of bringing the patient suspected of having tuberculosis in contact with his family physician, or, if need be, with a public chest clinic. When voluntary effort fails, public health authority must be employed (chart 3).

(6) *Education based on county survey findings:* The high spot of the survey program is the annual tuberculosis conference consisting of two sessions, one of which is conducted by the County Medical Society, the other being a general public meeting. The first scheduled annual tuberculosis conference under the auspices of the Delaware County Chest Survey Committee is to take place in October, 1945.[4]

In the scientific session the results of the chest surveys conducted in the county during the preceding year are discussed in considerable detail, with emphasis on follow-up, diagnostic problems and results of treatment in diagnosed cases. As far as possible the conference is concerned with local problems based on data gathered in local surveys. The scientific phase of the program climaxes the effort to educate the general practitioner in matters pertaining to tuberculosis and to equip him with the latest information for combating this disease.

[4] This meeting was held in Chester, Pennsylvania on October 11, 1945 and was known as the First Annual Delaware County Public Health Conference.

A statistical and narrative report emphasizing the scope of the local tuberculosis problem, the work accomplished to date and the plans for the coming year is the feature of the public meeting. This procedure assures the evolution of the chest survey program along scientific and progressive lines. It is also instrumental in encouraging public financial support, sufficient to make available to every resident in the county, at periodic intervals, an X-ray examination of his chest.

Such conferences result in higher standards of medical practice and in a better appreciation of the local tuberculosis problem.

FOLLOW UP OF SURVEY PATIENT AND FAMILY

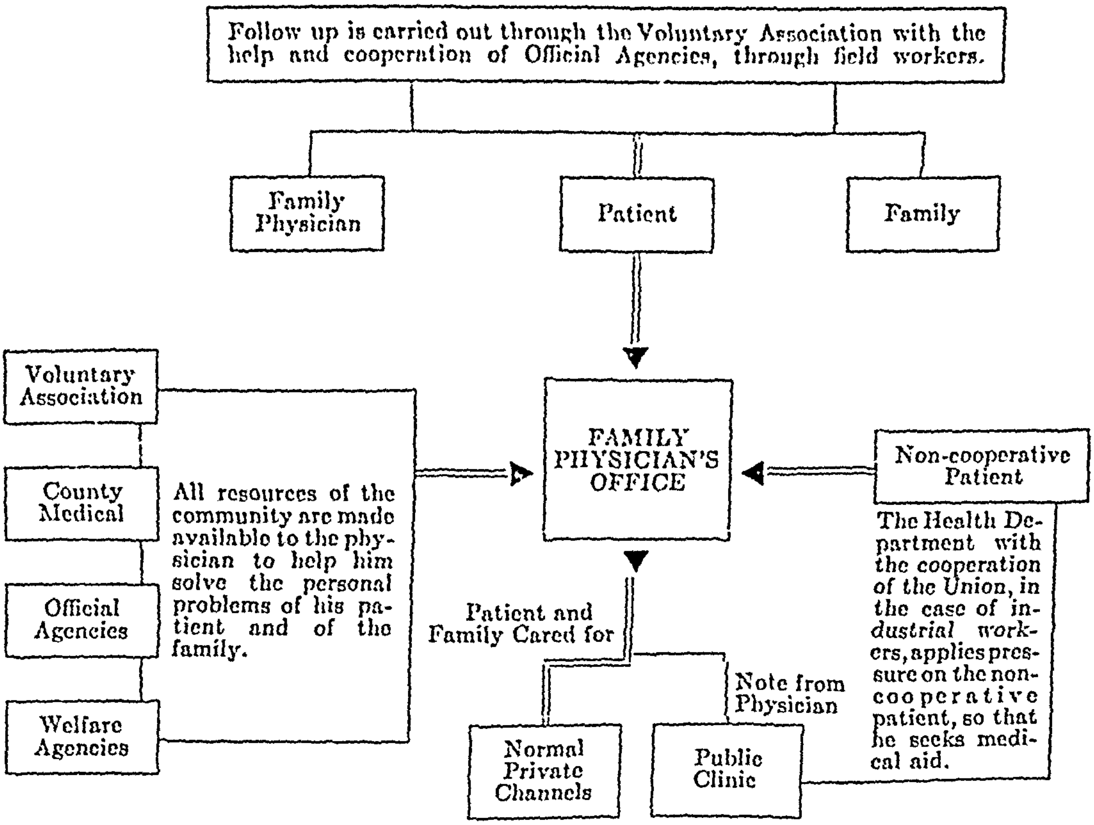


CHART 3. Follow-up is done in such manner as to bring the person suspected of having tuberculosis in contact with his own family physician and to strengthen physician-patient relationship. For survey purposes the family physician is the representative of the local health department and his private office a subcentre of activity in the diagnosis, prevention and control of tuberculosis.

(7) *The voluntary Association and community tuberculosis case-finding:* The voluntary Association has always occupied a vanguard position in the antituberculosis movement, energizing it and giving it direction. For years it has been a moving spirit in promoting mass X-ray studies all through the country. As an independent organization, supported by voluntary subscriptions, it can pioneer

new developments in tuberculosis control, support and conduct special studies, and generally carry on tuberculosis activities which official agencies (for various reasons) cannot do. It occupies an enviable position in any community tuberculosis case-finding program.

It is the logical agency to conduct an enlightened educational program in the county and to make chest surveys a vital and integral part of community health. As a part of a national organization, its facilities and trained personnel for such purposes are unexcelled. It is also admirably organized to carry out many technical phases of the survey program, and can well serve as headquarters to which requests for chest surveys among industrial workers and other groups in the county can be directed. Once a survey has been arranged for, the Association can take care of all details and act as an intermediary between the doctor and the public. It can forward reports to the family physician and patient and help generally with follow-up. With its independent program coördinated with those of the other groups (including those of the official agencies), the voluntary Tuberculosis Association can well serve as the spearhead of a locally organized case-finding program for the county.

(8) *Official health agencies and community tuberculosis case-finding:* Health departments, local, state and national, commonly referred to as official agencies, have a vital interest in tuberculosis case-finding. Routine chest X-ray examination is a highly desirable procedure because it can keep tuberculosis in the population at a minimum and relieve government of much expensive treatment in the future. However, government can best achieve its objective of eradicating tuberculosis through the close coöperation of its health officials, with the voluntary Tuberculosis Association, the local Medical Society and the family physician.

The official health agencies, at all levels, should actively support voluntary local efforts in tuberculosis case-finding, and join local groups in perfecting all inclusive tuberculosis control programs. Utilization of local talents and resources, and encouragement of maximum local initiative and responsibility should be the guiding principles. In keeping with this concept, health departments and local health officers should coördinate their efforts with those of other groups in the county, through the Chest Survey Committee. Health departments should not only participate in the deliberations of this Committee, and help in the formulation of plans, but should also take an active part in case-finding, in follow-up and in establishing and maintaining physician-patient relationship.

All the resources of government, technical, professional and financial, should be at the disposal of the Chest Survey Committee and utilized in complete harmony with efforts of local groups.

(9) *Industry and community tuberculosis case-finding:* Aside from the contribution industry can make to community health in supporting mass chest radiography, it also has an enlightened selfish interest. With tuberculosis eliminated, the efficiency of the workers will be greater, labor turnover will be less and lost time will be decreased. These factors reflect themselves in lowered costs of production.

Industry in coöperation with labor and other groups should make every effort to establish effective tuberculosis case-finding as an integral part of the general industrial program (14). By coördinating its activities with those of other agencies in the community, through the Chest Survey Committee, its problem can be greatly simplified and placed on a routine basis, and the effectiveness of the surveys enhanced. All that management has to do to conduct a survey of its employees is to make a formal request to the voluntary Tuberculosis Association for the survey; then, the machinery organized by the community for this purpose begins to function at once.

The Standing Committee on Industrial Relations, composed entirely of business and industrial representatives, studies the peculiar problems of mass chest radiography as they may affect business and industry, and makes recommendations accordingly to the Chest Survey Committee.

(10) *Labor and community tuberculosis case-finding:* Unions, through their health committees, must become actively interested in case-finding among their members and families. The Standing Committee on Labor Relations is composed solely of labor representatives and studies case-finding from the exclusive standpoint of the worker, and makes such recommendations to the Chest Survey Committee as promote the best interests of labor and protect the worker in his legitimate rights. It makes sure that information gathered in chest survey studies is treated as privileged information, divulged only to the family physician, and that the worker suspected of having disease is properly safeguarded in his job. When disciplinary measures become imperative in dealing with uncoöperative individuals, the safeguarding plan is carried out by the local health department, after due consultation with the Union.

(11) *The general public and community tuberculosis case-finding:* To be fully successful, mass case-finding must assume the character of a conscious community effort in which every county resident, every organized group, has an active part. Individuals not reached in industry or schools are organized in groups for survey purposes in and around local hospitals, schools, churches, community centres, union halls or other places.

Special efforts are made to reach groups with known high tuberculosis rates, such as the Negro and the underprivileged. Chest surveys are conducted on the spot, in surroundings familiar to the persons surveyed.

(12) *Welfare and health agencies and community tuberculosis case-finding:* Welfare and health agencies in the community sooner or later come into intimate contact with a considerable number of the residents in the county who are afflicted with tuberculosis. Their practical experience and potential help are made available to the Chest Survey Committee at the very outset of case-finding. Representatives of health and welfare agencies active in the county constitute a Standing Committee.

(13) *Financing of community chest X-ray surveys:* The financing of a continuous survey of more than 300,000 people is a difficult and complex undertaking. No one method will suffice. Funds can be secured from many sources, such as Christmas Seal sales, county, state and federal contributions, private gifts and by

direct payment from the person or group surveyed. The so-called "dollar chest X-ray," first made popular at the New York World's Fair in 1939, is a happy solution in this regard. It encourages payment by the person or group directly benefited, and holds the most promise of providing a continuous stream of funds for chest X-ray surveys in the county. It is the method of choice for all employed groups, schools, colleges, churches and lodges and, in fact, for any self-supporting group large enough to make the survey economically feasible.

As conceived in our plan, a charge of one dollar may be made by the Chest Survey Committee for each person surveyed. The sum of $1.00 has been found sufficient to pay all X-ray charges, including the cost of interpretation by competent physicians, provided the survey utilizes the facilities of the voluntary Association which can absorb much of the overhead. The dollar may be paid by the employer, employee or Union, or by any combination mutually agreed upon, in the case of industrial workers. In the case of other groups the dollar may be paid by the civic, school, church or fraternal organization, in which instances the individual may or may not contribute directly, in whole or in part. Under certain conditions, to further the idea, the voluntary Association may pay part or even all of the dollar.

It is certainly conceivable that the more the "dollar chest X-ray" idea becomes rooted in the consciousness of the public, the more chest surveys can be conducted in the county, and the more certain will mass X-ray case-finding become a fixed pattern in community health.

Public funds, restricted as they are by legislative controls, are better reserved for the unemployed, the migrant worker and the underprivileged. Christmas Seal funds, as heretofore, would be available for special studies in the education of the public and for the purchase and maintenance of equipment needed in mass radiography.

COMMENT

Has the community plan for mass chest radiography worked in actual practice? Has it produced the hoped for coöperation and coördination? The following typical examples are the answer.

(*1*) *Chest survey in schools:* The voluntary Association has been eager to educate the new generation of citizens to the appreciation of the value of chest X-ray examination in the prevention of tuberculosis. It is also eager to demonstrate the value of the method to local School Boards and health departments, to the end that chest X-ray surveys shall become a permanent feature of the school health program, with the cost ultimately paid for by the School Board or local health department. To accomplish this objective the voluntary Association has offered to X-ray free of charge, through the Chest Survey Committee, the pupils of every high school in the county. At the time of this writing all high schools in Delaware County have taken advantage of this plan. An understanding, nevertheless, has been reached that future surveys are to be paid for, at least in part, and ultimately entirely, by the School Boards. The voluntary Association, therefore, has aimed to keep moving to new and unbroken ground and thus fulfill its rôle of pioneer and spearhead.

It is planned in the future to invite the general public in the immediate neighborhood of the school to have free chest X-ray films taken at the school, on the day the school survey is conducted.

(2) *Chest survey of food handlers:* One of the most important features of a coordinated, organized community chest screening program is the teamwork and coöperation possible between the voluntary Association, the medical profession and the official agencies.

Not infrequently the official agency lacks funds for chest screening. Through tactful approach the voluntary Association and the medical profession can supply funds or personnel for the survey of certain groups of the population, and thus complete a phase of chest screening which is not only important to the local health department, but also fits in admirably with the rounded program of the Chest Survey Committee and the voluntary Association. For example, the Health Department of Chester, Pennsylvania ruled that restaurant proprietors must have all food handlers X-rayed, in order that the restaurateurs might obtain 1945 licenses.

Free chest X-ray examinations under the auspices of the voluntary Association, Health Department and County Medical Society were made available to all food handlers on three successive days in the Chester Armory. Twenty-three hundred and sixty-five free chest X-ray examinations were made. The X-ray films were read and interpreted by the Committee of Interpreting Physicians from the local Medical Society and the results were forwarded to each person's family doctor. The entire cost of the project was borne by the voluntary Association.

The local press featured this X-ray survey and gave it wide coverage, commented on it with favorable editorials, and stressed the fact that it was a coöperative effort on the part of the entire community. The public was fully aroused as to the significance and meaning of the undertaking, and the educational value was tremendous. As a result of this particular survey 20 persons were found to have clinically significant tuberculosis.

It is an excellent example of coöperation between the public health authorities, the voluntary Association and the medical profession.

(3) *Chest survey in industrial plants:* The management of a large industrial concern in Delaware County became interested in a chest survey of its employees and contacted the secretary of the Delaware County Tuberculosis and Health Association (who is also secretary of the Chest Survey Committee of the County). Arrangements were made and the survey completed within a short time. Reports were then sent to each person examined and to his or her family physician. Regarding those showing disease, a brief letter was sent to the individual explaining the facts and advising him to consult his family physician. Twenty-one persons were found to have clinically significant tuberculosis and were placed under the care of their own physician.

The films were interpreted by the members of the Committee of Interpreting Physicians, each one of whom was a practicing radiologist or tuberculosis specialist in Delaware County. The results were forwarded to the secretary of the Chest Survey Committee for the purpose of distribution. When the problem

seemed urgent, information was conveyed to the secretary by telephone and written reports followed. A summary of the findings, as well as some of the more important films, were also filed with the secretary of the Chest Survey Committee for future use in scientific and lay programs.

The technical and financial details of the transaction were handled by the secretary of the Delaware County Tuberculosis and Health Association in his capacity of secretary to the Chest Survey Committee. Everything worked smoothly because each step in the survey was well planned in advance.

The cost of the survey was solved in the following manner: Management paid one dollar for each of its 971 employees who were considered permanent. The Delaware County Tuberculosis and Health Association, as a public service, paid for all employees whom management considered temporary, 300 of them, employees who had been with the company six months or less. In this instance the Employees Beneficial Society, representing labor, assisted and coöperated to the fullest extent. So also did the medical department of the plant.

The educational value of the survey was of considerable importance. Reports relating to their own patients were sent directly to 185 different practicing physicians who were in this way made tuberculosis-conscious; and the lesson of the existence and importance of significant tuberculosis in ostensibly healthy persons was impressed upon them. Personal contacts and telephone calls were outstanding factors in bringing patient and family physician together. The family physician held the centre of activity throughout the survey and his office was the first destination of the person with suspected disease. For survey purposes he was the representative of the local health department. The physicians responded accordingly and coöperated whole-heartedly.

Newspaper publicity was also used skilfully, and the entire community was made aware of the existence of a tremendous public health movement in their midst, namely the eradication of tuberculosis. Furthermore, the privacy and rights of the persons examined were scrupulously guarded all through the survey. Only the patient and family physician knew officially the result of the examination. The plant physician received only a statistical report informing him in general terms of the survey results. No names were forwarded. Everyone cooperated and everyone profited.

These three examples in widely different fields well illustrate the fundamental approach to chest X-ray surveys in the county, and how flexible the program is intended to be. Applied intelligently and selectively, as more funds become available through governmental agencies and other sources, chest surveys can be conducted on an ever increasing scale with every promise of making the procedure an established part of community health.

SUMMARY

A practical plan of procedure for tuberculosis case-finding by mass radiography has been evolved in Delaware County, Pennsylvania under the guidance and leadership of the Delaware County Medical Society.

The program is organized as a coöperative community undertaking of all local

groups interested in tuberculosis case-finding. It is an example of coördinated solutions of such complex problems as medical economics and ethics, and relationships between the practicing medical profession, the Departments of Health, the voluntary Tuberculosis Association, the health and welfare agencies and other groups in the county concerned with the eradication of tuberculosis.

The work of the various groups is coördinated through a County Chest Survey Committee on which all have representation. This Committee discusses principles of coöperation, studies reports and is charged with the responsibility (through the coöperating agencies) of developing and supervising an over-all tuberculosis case-finding program for the whole county. All major decisions, however, are subject to approval by the County Medical Society, the voluntary Tuberculosis Association and the Departments of Health, to establish harmony of purpose and avoid duplication of effort.

Every phase of the program has been worked out with a view to maintaining physician-patient relationship, to protecting the privacy of the individual examined and to mobilizing and activating the latent determination of the public to eradicate tuberculosis from its ranks. It is also intended as a demonstration that private medicine is capable of providing leadership and of successfully giving effect to large scale public health undertakings. When properly organized, case-finding can become a community movement under local guidance and responsibility, with government coöperation and help.

This plan has been in operation since the fall of 1943, and mass chest radiography in Delaware County has grown rapidly since, limited only by the available facilities and financial resources.

This approach to mass chest radiography, modified to meet varying local conditions, appears adequate for immediate application to other counties in the country.

SUMARIO

En el Condado Delaware, de Pennsylvania, han elaborado un plan práctico para el descubrimiento de casos de tuberculosis mediante la radiografía en gran escala bajo la dirección de la Sociedad Médica del Condado.

El plan constituye un esfuerzo colectivo en que cooperan todos los grupos interesados en el problema en la localidad, aportando un buen ejemplo de las soluciones coordinadas que pueden ofrecerse a problemas tan complejos como son la economía médica y la moral profesional, y las relaciones que deben existir entre la profesión médica, los Departamentos de Sanidad, la Asociación Antituberculosa, los organismos de salud y beneficencia y otros grupos interesados en la erradicación de la tuberculosis.

La labor de los varios grupos es coordinada por una Comisión de Encuesta Torácica en que están todos representados. Dicha Comisión discute los principios de cooperación, estudia los informes a medida que se van recibiendo y tiene la obligación (por conducto de los organismos cooperativos) de elaborar y vigilar un plan general de descubrimiento de casos de tuberculosis para todo el Condado. Sin embargo, todos los acuerdos principales tienen que contar con la aprobación

de la Sociedad Médica, la Asociación Antituberculosa y el Departamento de Sanidad a fin de armonizar los propósitos y evitar duplicación de esfuerzos.

Todas las fases del programa han sido estudiadas con mira a mantener la relación entre médico y enfermo, de proteger el secreto del individuo examinado y de movilizar y activar la determinación del público de erradicar la tuberculosis en sus filas. También se propone servir de demostración de que la medicina privada es capaz de dirigir y llevar a cabo con éxito empresas sanitarias en gran escala, así como de que, debidamente organizado, el descubrimiento de casos puede convertirse en un movimiento colectivo bajo orientación y auspicios locales con el concurso y ayuda del Gobierno.

Este plan está en funcionamiento desde el otoño de 1943 y desde entonces la radiografía torácica en uso en dicho Condado ha tomado cada vez más auge limitándola únicamente los medios y recursos económicos disponibles.

Este empleo de la radiografía torácica, modificado para ajustarse a las condiciones de cada localidad, parece prestarse para aplicación inmediata a otros distritos del país.

REFERENCES

(1) Evolution of Tuberculosis as Observed during Twenty Years at Lymanhurst, Minneapolis Board of Public Welfare, Minnesota Public Health Association, 1921–'41.

(2) Hilleboe, H. E.: Federal Tuberculosis Control Division Organized, N. T. A. Bulletin, August, 1944, p. 319.

(3) Wing, Virginia: Community Health Revival, Survey Midmonthly, January, 1944.

(4) Vaughan, H. F., and Douglas, B. H.: Intensive case finding work on tuberculosis, J. A. M. A., September 4, 1937, *109*, 771.

(5) Long, E. R.: Discussion of paper by Vaughan and Douglas (4).

(6) Trail, R. R., *et al.*: Mass Miniature Radiography: A Practical Handbook, London, J. & A. Churchill, Ltd., 1943.

(7) Hilleboe, H. E., and Morgan, R. H.: Mass Radiography of the Chest, Chicago, Year Book Publishers, 1945.

(8) Geib, L. O., and Vaughan, H. F.: The physician as health worker, J. A. M. A., August 8, 1931, *97*, 366.

(9) Riley, R. H.: Preventive medicine, J. A. M. A., August 24, 1935, *105*, 555.

(10) Bauer, W. W.: The physician's place in the health program, J. A. M. A., August 15, 1936, *107*, 485.

(11) Myers, J. A.: President's New Year Message, Dis. of Chest, 1945, *11*, 93.

(12) Plunkett, R. E.: The rôle of the private physician in tuberculosis control, Health News, December 18, 1944, *21*, 222.

(13) Parran, Thomas: Surgeon General U.S.P.H.S., Letter to Editor, Philadelphia Medicine, January 6, 1945, *40*, 609.

(14) Hilleboe, H. E., and Gould, D. M.: Conquest of tuberculosis in industry, J. A. M. A., May 27, 1944, *125*, 241.

THE ST. LOUIS COUNTY TUBERCULOSIS SURVEY

ROBERTS DAVIES,[1] G. A. HEDBERG[1] AND MARIO FISCHER[2]

On September 9, 1943 we began a tuberculosis survey of the whole population of St. Louis County. This county has an area of approximately 6,850 square miles and a population of 207,000. Almost half the population (101,000) lives in the city of Duluth. There are five other towns of over 5,000 population. The corrected tuberculosis death rate, calculated for St. Louis County residents for 1942, was 37.2 per 100,000. This included all known deaths of county residents reported as occurring outside the limits of the county and excluded nonresident deaths from tuberculosis that took place within the county.

ORGANIZATION

The policy-making body for the tuberculosis survey, as well as for all other regional antituberculosis efforts in the county, is the St. Louis County Advisory Committee on Tuberculosis, appointed by the County Board of Commissioners. This Committee includes representatives of the Minnesota Department of Health, the St. Louis County Health Department, the various town and village health departments, Nopeming Sanatorium, the St. Louis County Welfare Department, the Tuberculosis and Health Association of St. Louis County, the St. Louis County Medical Society and the second and tenth district nurse sassociations. In addition, the Committee includes such other physicians in the county as are especially interested in tuberculosis. We believe this Committee has been important in the success of the survey because it has provided for the expression of all shades of opinion and has thereby earned for its final decisions the support of all interested groups and individuals in the county.

The survey has been directed by the medical staff of Nopeming Sanatorium and made with a photofluorographic unit housed in a bus-type vehicle. The unit takes 4 x 5 inch films and uses a rotating anode tube. The transformer has a capacity of 200 milliamperes and is supplied by a gasoline driven generator housed in a trailer. The unit is staffed by a public health nurse and a technician-chauffeur.

If a large percentage of any group is to be examined voluntarily, it is essential that the survey be explained by word of mouth to all the members of the group and that they be given a chance to ask questions. Our presentations emphasize, among other things, that tuberculosis is a contagious disease; that early tuberculosis usually produces no alarming symptoms; that X-ray examination of the chest is the only reliable method of detecting early tuberculosis; that a photofluorogram is a screening medium and not comparable to X-ray examination with a full-size film; that there is no charge for the examination; and, finally, that the private physician is a key figure in the program who will receive all X-ray reports and interpret them to his patients.

[1] Nopeming Sanatorium, Nopeming, Minnesota.
[2] Director of Public Health, City of Duluth, Minnesota.

For the organization of an industrial survey it is highly desirable that the examination be requested by a group representing the employees such as a labor union. Employees are not likely to volunteer for any physical examinations arranged by management alone. Whenever a request chances to come first from management we ask that some group representing the employees likewise request the survey before we arrange for it. All explanations of the survey are given in detail, both to the management and to all the employees concerned. We stress the fact that all reports of findings are confidential and will not be available either to management or to a labor union. The details of the survey procedure, even to the minutiae, are worked out as carefully as possible beforehand to minimize loss of time. It has been possible in some circumstances to average only five minutes' loss of work time per individual examined. Such an accomplishment holds great appeal for management which, to date, has absorbed these time losses with full pay in every instance.

In the organization of complete community surveys, every effort is made to have the community assume both the responsibility and the credit for success of the survey. The first step is to call an open meeting to which all persons interested in tuberculosis control are individually invited. The rationale of the survey and its methods are presented. Those present are asked to select a chairman for the campaign. The chairman then appoints subcommittees to arrange for publicity, canvassing and enlisting of volunteers to serve as clerks, dark-room assistants and hostesses.

The publicity chairman is urged to use all publicity facilities in the community such as newspapers, radio and motion picture trailers. Pamphlets, posters, displays and material for newspaper stories and radio talks are furnished him. Speakers and motion picture films are provided for all civic groups such as Rotary and Kiwanis Clubs, Parent-Teacher Associations, lodges, church groups, labor unions, commercial clubs, schools and various foreign language organizations. The clergy are interviewed and asked to mention the survey in church and to support it in private conversations. All the doctors in the community are interviewed and their support enlisted.

In most communities the canvassers have been organized around a group of Victory Aides, a part of the Civilian Defense Program. These women are schooled, as well as we can possibly do it, on tuberculosis and its prevention and the significance and methods of the survey. They are given answers to the most commonly encountered objections to routine X-ray examination. As canvassers, they visit personally every house in their district and explain the survey to everyone. At the same time they make a complete census record by households for use of the public health nurse attached to the mobile unit.

On the basis of this census, post-cards making appointments for examination are mailed each day to some 300 to 400 persons. If an individual fails to keep the appointment so made, another card making another appointment is mailed. If there is still no response the public health nurse with the unit or a nurse from the local health department makes a home call.

The mobile X-ray unit is usually located at a public building, such as a school,

where there are dressing rooms and a room for clerical assistants. If no public building is available, a private home may be utilized. Occasionally the unit operates without any adjacent building since small dressing units are available in the truck. It is important that the unit be within easy reach of all the people to be examined. In towns we arrange the placement of the unit so that no one need walk farther than two blocks for an examination. In the country the limit is half a mile. In exceptional circumstances transportation by car is provided for clients. It is essential that all circumstances be so arranged as to make it distinctly easier for the individual to accept examination than to refuse it.

All films are developed and interpreted at the Sanatorium. A report on every film is sent to the individual's own physician. If any evidence of tuberculosis is found, a letter is also sent to the patient asking him to see his doctor and enclosing a requisition for a single 14x17 inch chest film to be taken without charge to the patient. The doctor taking the film is paid $3.50 for it, and all films are sent to the Sanatorium for interpretation. If the individual ignores this notice, a public health nurse from the Sanatorium calls on the patient to urge him to see his physician and have a film made. She also obtains a history of any symptoms and present or past chest disease and, if possible, obtains sputum for laboratory examination. Culture as well as microscopic examination of sputum specimens is done routinely on all persons showing any evidence of tuberculosis, even if the lesion appears roentgenologically to be unimportant. If the 14 x 17 inch X-ray film of the chest shows any evidence of activity such as cavitating or exudative lesions, if tubercle bacilli are found in the sputum, or if the private physician feels there is evidence of activity on clinical grounds, the patient is admitted to the Sanatorium for further study. Persons with evidence of reinfection tuberculosis who are not admitted are followed by the Sanatorium outpatient department so long as they continue to live in St. Louis County. No matter how thoroughly healed a lesion may appear to be, the patient is never discharged from observation.

RESULTS

The 4 x 5 inch photofluorographic films have been found very satisfactory for screening purposes. On approximately 1 per cent of the films taken, a repeat film has been ordered because the original was technically unsatisfactory. In a good many cases such unsatisfactory films are the result of errors such as double exposures or unexposed films due to failure to remove the protecting slide of the film holder. On approximately 4 per cent of the films taken, repeat 14x17 inch films are ordered on the basis of definite or suspected lesions. Roughly, 10 per cent of these repeat films are entirely negative for both tuberculous and nontuberculous lesions. On the basis of a review of several hundred cases in which previous or subsequent full-size films were available for comparison with the miniature film, we feel that about 10 per cent of minimal, discrete, apical, fibroid infiltrations are missed on the 4 x 5 inch film. To our knowledge we have not yet missed an active tuberculous lesion.

In one year of operation 34,054 persons were examined. Five hundred sev-

enty-nine persons (1.7 per cent) showed lesions which we consider significant tuberculosis. This includes all apparently tuberculous lesions regardless of extent or evidence of activity with the single exception of an apparently thoroughly healed primary infection, such as a calcified primary complex. Of these 579 cases of tuberculosis, 385 (66.5 per cent) had minimal disease, 155 (26.8 per cent) had moderately advanced disease and only 39 (6.7 per cent) had far advanced disease.

The determination of the activity of such a large number of tuberculous lesions presents considerable difficulty. We do not have a sufficient number of sanatorium or hospital beds to permit us to admit all those with apparently tuberculous disease for intensive study. Even if enough beds were available it would probably be unwise as well as unduly expensive to study every case as an inpatient. Many people who are admitted for a short period of study and then discharged as having apparently inactive tuberculosis, feel that their time and money have been wasted by unnecessary hospitalization. When they return home some such patients share their opinion with their neighbors. In addition, we have noticed repeatedly that if a comparatively large number of persons are asked to come in to the Sanatorium while a community survey is in progress, we then meet with more refusals among the unexamined fraction of the community. With these facts in mind, we have asked for sputum examinations and repeated X-ray examinations on all persons showing any X-ray evidence of pulmonary tuberculosis more than a calcified primary complex, but we have advised sanatorium admission only if there were suggestive symptoms, X-ray evidence of exudative disease or cavitation, or tubercle bacilli in the sputum or gastric contents. Such a procedure no doubt leaves a few cases of active but presumably noninfectious disease in the community, but any of these that are progressive will be picked up on subsequent examinations.

Forty-two of the 579 persons with presumably tuberculous lesions have been admitted to the Sanatorium. Twelve of these were discharged after a short period of observation and study because activity could not be demonstrated, and 30 had definitely active disease. In 8 additional persons, who have not been admitted to the Sanatorium, the findings permit a definite diagnosis of active disease. In all, definitely active tuberculosis has been demonstrated in 38 persons. This is 0.1 per cent of the group examined and 6.6 per cent of those having presumably tuberculous lesions, exclusive of healed primary complexes. Eight (21 per cent) of the 38 cases with definitely active disease had minimal pulmonary involvement, and 25 (66 per cent) showed no tubercle bacilli on microscopic examination of all sputum raised over a five-day period. In addition to the 38 cases with definitely active tuberculosis, there are 24 others with tuberculous lesions which are suspected but not yet proved to be active. None of these have yet been admitted to the Sanatorium.

Of the 8 definitely active cases that have not been admitted to the Sanatorium, 6 were either not county residents or left the county before admission could be arranged. These persons have been reported to the health officer at their present residence. One case is under the care of a private physician and has had re-

peated negative sputum examinations. The other person is a child with active primary tuberculosis, living in an adequate home without any other children in the household and under the supervision of one of our tuberculosis clinics.

Of the 21 cases classified as suspiciously active, 14 either are nonresidents or left the county before adequate examination could be arranged. Two cases are under the supervision of private physicians who consider the disease inactive. Eight persons who are county residents and not known to be under a physician's care have so far had inadequate follow-up examinations. Most of these were discovered relatively recently.

Abnormal cardiac shadows, pulmonary emphysema, atypical pneumonia and findings suggestive of bronchiectasis and of enlarged thyroid glands were frequent. A very few cases of aneurysm, diaphragmatic hernia, lung abscess and pulmonary infiltrations resembling sarcoidosis were found. The incidence of situs inversus was approximately one in 10,000. Sixteen persons or approximately one in 2,000 showed chest tumors, including tumors of the thoracic cage. Three of these tumors were very probably bronchogenic carcinoma, although, to our knowledge, in only one case was the diagnosis confirmed. In a good many of these nontuberculous conditions the diagnosis was of great importance to the patient and was not suspected until the miniature film was taken.

Although we have not yet made a complete study of the prevalence of tuberculosis and other chest diseases by age, sex and occupation, we have limited information on the incidence of tuberculosis in three occupational groups. In 9,141 examinations of students, faculty and nonacademic school employees, chiefly at the high school and college levels, the incidence of significant tuberculosis was only 0.3 per cent, and only 0.04 per cent had active disease. In a group of white-collar workers, 1,787 examinations disclosed 1.8 per cent with significant tuberculosis and 0.2 per cent with active disease. From 5,418 films taken of employees in heavy industry, there were 1.7 per cent with significant tuberculosis, and active disease occurred in 0.15 per cent.

Seventeen thousand one hundred and eighty-four of the total of 34,054 films were taken in surveys of special groups such as schools, industries and offices. The other 16,870 were taken in complete community surveys which covered 1,000 square miles of the county. The completeness of community examination varied from a low of 65 per cent of the population having miniature films to a high of 95 per cent with such examinations. The median coverage in all community surveys was 87 per cent examined with miniature films. An additional 6.5 per cent of the population gave a history of having had a satisfactory chest X-ray examination within a year, and in about two-thirds of these cases we actually know that such a film was taken. In the most complete survey, the town of Ely with a population of over 6,000, 99.4 per cent of the population were either examined by our mobile unit or had a recent 14 x 17 inch film, mostly in an industrial survey which was done almost concurrently. In all the surveys, residents of the community who could not possibly be examined, such as bed-ridden invalids and persons temporarily away from home during the time of the survey, were tabulated in the unexamined fraction as were also infants who did not have

a film taken. In these community surveys 2.4 per cent of the population examined showed significant tuberculosis, and 0.1 per cent had active disease.

COST

The cost of this survey for one year was $19,144.85. Salaries and traveling expenses account for $10,589.95 of this amount. Not included in the calculation of cost are the original cost of the equipment, the depreciation of the equipment and charges for the services of volunteer helpers. Most of the latter were persons who served entirely without compensation. However, some were employees of health departments and other governmental units who gave a great deal of time and effort when the mobile unit was operating in their communities. They were not hired for that purpose nor did their employers hire any replacements to carry on their usual work.

With the exceptions noted, we believe all cost are properly credited including operating costs for the unit, cost of X-ray tube replacement, and cost of salaries and materials used in developing and interpreting the films and in conducting correspondence and keeping records. The cost of follow-up to insure that all persons showing evidence of tuberculosis had 14 x17 inch chest films and any other necessary examinations is also included as is the cost of the 14 x 17 inch films taken by local physicians at $3.50 each.

The cost per individual examined was 56 cents. The cost per case of tuberculosis discovered was $33.07. The cost per active and suspiciously active case discovered was $308.79 and the cost per definitely active case was $503.81. If the cost of follow-up is deducted, these items become, respectively, 43 cents, $25.31, $236.34 and $385.61. These costs may be compared to $171.00 reported by Plunkett in 1939 as the cost of finding an active case of tuberculosis by examination of contacts and persons with symptoms in New York State Health Department clinics and to $103.09 reported by Morse in 1941 as the cost of finding an active or suspiciously active case of tuberculosis in Wisconsin. Our costs per case contain items such as costs of clerical work and of follow-up that may have been omitted in these other calculations, and it is altogether probable that the cost of tuberculosis case-finding, like the cost of most everything else, has increased considerably since 1939 and 1941. However, it seems evident and reasonable that the costs of case-finding by examination of apparently healthy persons in the general population will be higher than if efforts are directed entirely to persons with symptoms and to contacts of known cases. Such costs can more properly be compared to the much greater costs which result from permitting cases of active tuberculosis to remain undiagnosed in the community. With the use of more efficient equipment, such as 70 mm. photofluorographic units equipped with the Morgan photo-timer and the Fairchild camera, the volume of work per day should be considerably increased and the unit cost of photofluorographic surveys proportionately decreased.

COMMENT

The aim of antituberculosis work should be the eventual eradication of the disease. The great decline in tuberculosis mortality observed in the past fifty

years has produced an optimism and complacency which are probably unjustified. The observation of Frost that declining mortality and morbidity mean that the disease is unable to reproduce itself is axiomatic, but the assumption that control measures are therefore adequate and will eventually eliminate the disease is by no means sound. It would appear more likely that, as cases diminish, further improvement will become more difficult and that a level will be reached at which control measures now in use will be reasonably effective in preventing increases in tuberculosis, but will not succeed in appreciable further reduction. It would seem that that stage is near, since the past ten years have shown a deceleration in the rate of decline of mortality in the United States, and the past two years have shown increases in mortality in several states.

The only weapons of proved and generally accepted value against tuberculosis are discovery, isolation and treatment of all active cases. The deficiencies of a case-finding program based wholly on the examinations of persons with pulmonary symptoms and of contacts of known cases have been appreciated for some years past. Symptoms alarming enough to prompt an individual to seek medical attention usually occur only when tuberculosis is so advanced that there has already been ample opportunity for the infection of others before the diagnosis is made. Examination, even of intimate contacts, is commonly incomplete because of the difficulties in securing adequate coöperation. The fact that over half of the persons admitted to sanatoria give no history of contact with an antecedent case makes one feel that, even if complete examination of intimate contacts were possible, it might be rather ineffective, both because obvious tuberculosis may develop many years after the contact is broken and because rather casual contacts may be of considerably greater significance than is ordinarily appreciated. It seems evident from these considerations that broader and more intensive case-finding efforts are needed.

Arguments against wide-spread use of photofluorographic surveys to extend case-finding efforts have been advanced on two bases; first, that Mantoux surveys with X-ray examination of positive reactors are preferable and, second, that such surveys are a step toward undesirable socialization of medical practice.

It is obvious that tuberculin tests add a great deal to the value of a tuberculosis survey, and we use them constantly in the study of patients with suspicious lesions found on the miniature film. We have not used a Mantoux test routinely in our surveys because, on the basis of our experience with Mantoux surveys in the past and from similar experiences of others, we have felt that it would increase the cost of the survey, the number of refusals and the time required for each examination, thus reducing the number of people that could be examined each year. In this connection, we should remember that a Mantoux survey, with X-raying of positive reactors only, will not, in fact, identify all persons who have been infected with tubercle bacilli. It has been well established that, unless reinfection occurs, a certain number of people (estimated variously from 5 per cent to 25 per cent) who have been infected with tubercle bacilli will eventually lose their ability to react to dosages of tuberculin ordinarily used in surveys. In addition, a survey with X-ray examination of tuberculin reactors only will miss

many cases of abnormal hearts, chest tumors, bronchiectasis and other nontuberculous chest diseases that are discovered as an incidental but worth while by-product of a photofluorographic tuberculosis survey. While such nontuberculous conditions are not our chief concern, they are frequently of great importance to the patient and are of some considerable importance from a public health standpoint.

The argument that such surveys of apparently well people are an undesirable step toward socialization of medical practice seems singularly unimpressive to us. In the first place, a job well done, no matter by whom, does not make people dissatisfied with our present system of medical care. It is when we fail, or appear to fail, to solve a problem that the proponents of state medicine pick up an impressive argument. In the second place, such surveys need not be made by a governmental agency. They may just as well be sponsored by a medical society as in the Meeker County tuberculosis survey in Minnesota. In the third place, a program, organized as the St. Louis County survey is, increases to a considerable extent the practice of the private physician. The people examined must all get their reports from their own physician and will no doubt consult him about other health problems at the same time. Those who are found to have nontuberculous chest disease will need advice and treatment which the large majority will get from their own doctors. From a financial standpoint, the roentgenologists and any other physicians with X-ray equipment profit most, since all persons with definite or suspicious pulmonary lesions require 14 x 17 inch chest films, and all those with tuberculous lesions will require such films at regular intervals throughout their lifetime.

We feel that the wide-spread examination of apparently healthy people by photoroentgenological methods is a most important weapon against tuberculosis. The ideal, which we hope to make a reality in our county within a year or two, would appear to be surveys of the whole population on a complete community basis and repeated at intervals of perhaps two years. That such surveys can be made has been demonstrated, both by us and by others. In a subsequent paper we will present evidence indicating that such surveys are actually an effective method of tuberculosis control.

SUMMARY

1. A review of the first year's operation of the St. Louis County Tuberculosis Survey with a mobile photoroentgen unit has been presented including organization, results and costs.

2. Thirty-four thousand and fifty-four persons were examined, of whom 579 (1.7 per cent) had significant tuberculous lesions. Thirty-eight (0.1 per cent) had definitely active pulmonary tuberculosis, 24 had suspiciously active tuberculosis and 42 were admitted to the Sanatorium.

3. Two-thirds of the active cases had negative sputum on microscopic examination of five concentrated twenty-four hour specimens.

4. One thousand square miles of the county have been covered by complete community surveys. Examinations were made of 16,870 persons or a median of 87 per cent of the communities surveyed.

5. The cost of this survey for one year was \$19,144.85 or 56 cents per person examined, \$33.07 per significant case of tuberculosis found and \$308.79 per definitely or suspiciously active case.

6. We believe that the photoroentgen survey and more especially the complete community survey are practical and important weapons in the fight against tuberculosis.

SUMARIO

1. Esta reseña describe el resultado obtenido durante el primer año de una encuesta tuberculosa en el Condado St. Louis con una unidad fotorroentgenográfica movible, comprendiendo organización, resultado y costo.

2. De 34,054 personas examinadas, 579 (1.7%) mostraron lesiones tuberculosas de importancia. En 38 había tuberculosis pulmonar netamente activa, en 24 tuberculosis activa sospechosa y 42 fueron recibidos en el Sanatorio.

3. Dos terceras partes de los casos activos mostraron esputo negativo al examen microscópico de 5 ejemplares de 24 horas concentrados.

4. Más de 1,600 kilómetros del Condado fueron cubiertos por completas encuestas colectivas, examinándose a 16,870 personas, o sea en conjunto 87% de la población comprendida.

5. El costo de esta encuesta durante un año fué de \$19,144.85, o sea: \$0.56 por persona examinada, \$33.07 por cada caso significativo de tuberculosis descubierta y \$308.79 por caso activo comprobado o sospechoso.

6. La encuesta fotorroentgenográfica, y más en particular la encuesta colectiva completa, son armas prácticas e importantes en la lucha antituberculosa.

The success of this survey was dependent on the whole-hearted coöperation of literally hundreds of people, only a few of whom can be mentioned here. We would like to express our thanks and appreciation to the following, whose help was especially generous and important: Dr. B. J. Terrell, Dr. E. W. Henry, Dr. C. H. Magney, Dr. H. N. Sutherland, Dr. J. P. Grahek, Dr. R. W. Backus, Mr. Paul VanHoven, Mr. William T. Bates, Mrs. Austin Lathers, Mrs. M. J. Fleming, Mrs. Ina Metso, Miss Josephine Lepak, Miss Elsie Keskinen, Miss Agnes E. Anderson, Miss Leah Keable, Miss Catherine Vavra, Mrs. Ruth Jensen, Miss Arlene Hayden, Miss Evelyn Carlson and Miss Rose Nemanich.

REFERENCES

(1) Bridge, E.: Case-finding with fluoroscopic roentgenography, Am. Rev. Tuberc., *1940*, *42*, 155.
(2) Industrial chest X-ray survey, Bull. Academy Med. of Cleveland, March, 1944.
(3) Widespread tuberculosis surveys, Bull. Canad. Tuberc. A., 1943, *20*, 7.
(4) Behind the scenes of a city-wide survey, Bull. Canad. Tuberc. A., June, 1944.
(5) Davies, R: Complete community surveys for tuberculosis, Journal-Lancet, 1941, *61*, 113.
(6) Davies, R., and Scherer, C. S.: Tuberculosis survey of an entire community, Am. Rev. Tuberc., 1939, *39*, 778.
(7) Davies, R., and Robb, C. S.: Community survey for tuberculosis, Am. Rev. Tuberc., 1941, *44*, 118.
(8) Davison, R., and Troy, E. P.: Experiences in a program for the control of pulmonary tuberculosis in Chicago, Dis. of Chest, 1944, *10*, 54.

(9) Dempsey, M.: What is happening to the tuberculosis death rate? Am. Rev. Tuberc., 1944, *50*, 556.
(10) Douglas, B. H., and Birkelo, C. C.: The miniature X-ray film of the chest, Am. Rev. Tuberc., 1941, *43*, 108.
(11) Edwards, H. R., Preas, S,. Downes, J., and Robins, A.: Tuberculosis case-finding—an X-ray survey of 28,331 trade union members in New York City, 1939, Am. Rev. Tuberc., 1941, *43*, 491.
(12) Edwards, H. R.: The cost of tuberculosis control in the Department of Health, New York City, 1940, Milbank Memorial Fund Quarterly, 1943, *21*, 64.
(13) Ferguson, R. G.: Personal communication, November, 1943.
(14) Filek, A.: TB in Wisconsin, N. T. A. Bull., August, 1944.
(15) Frost, W. H.: How much control of tuberculosis?, Am. J. Pub. Health, 1937, *27*, 1.
(16) Hedberg, G.A.: The St. Louis County program of tuberculosis control, Minnesota Med., 1945, *28*, 122.
(17) Hilleboe, H. E.: The tuberculosis control program of the United States Public Health Service, Am. J. Roentgenol., 1943, *50*, 214.
(18) Mason, M. W.: The adequacy of the photofluorographic method of chest survey, Ohio State M. J., 1943, *36*, 830.
(19) Mattison, B. F.: Some factors affecting the early diagnosis of pulmonary tuberculosis, Am. J. Pub. Health, 1944, *34*, 1163.
(20) Morse, M. S.: Tuberculosis costs and control, Wisconsin M. J. 1941, *40*, 226.
(21) Plunkett, R. E.: Case-finding—an evaluation of various techniques, Am. Rev. Tuberc., 1939, *39*, 256.
(22) Potter, H. E., Douglas, B. H., and Birkelo, C. C.: The minature X-ray chest film, Radiology, 1940, *34*, 283.
(23) Rich, A. R.: The pathogenesis of Tuberculosis, Charles C Thomas, Baltimore, 1944, 212–215.
(24) Trail, R. R., Trechard, H. J., Anson, C. E. H., Scott, L. G., Clive, F. T., Evans, A. C., Kennedy, J. A., Pierce, J. W., Price, C. F., and Warner, H. A.: Mass miniature radiography in the Royal Air Force, Brit. J. Tuberc., and Dis. of Chest, 1944, *38*, 116.

THE COMBINED ACTION OF P,P'-DIAMINODIPHENYLSULFONE AND IMMUNIZATION IN EXPERIMENTAL TUBERCULOSIS[1]

BEN C. SHER AND JOHN M. KLOECK[2]

The combined effect of chemotherapy and immunization on animals infected with virulent tubercle bacilli is of particular interest because the conditions simulate human reinfection tuberculosis. Little attention has been given to this problem thus far. Steenken *et al.* (1) have reported on the effects of promin and immunization in guinea pigs, with the conclusion that the combined effects induced a greater inhibition of the tuberculous process than promin alone.

The purpose of this paper is to report the results obtained with a different agent (p,p'-diaminodiphenylsulfone) and immunization, with additional controls. Under the conditions of our experiments the results obtained are considerably at variance with those previously reported.

METHODS

Animals and controls: Seventy female guinea pigs approximately 8 weeks old were adjusted to the routine of the animal room for one month. These animals were then divided into four groups as follows:

Group A: Ten untreated controls, infected with 0.0001 mg. Corper's H4008B tubercle bacilli. (Control group.)

Group B: Twenty guinea pigs infected as in group A and three days later treated orally with 0.1 g. diaminodiphenylsulfone, daily. (Treated group.)

Group C: Twenty guinea pigs immunized with 0.0005 mg. of Corper's human avirulent strain; thirty-three days later infected as in group A, and untreated. (Immunized control group.)

Group D: Twenty guinea pigs immunized and infected as in group C, then three days after infection treated with 0.1 g. diaminodiphenylsulfone daily. (Treated immunized group.)

Immunization: The immunizing and infecting organisms were prepared by suspending weighed quantities of the tubercle bacilli which had been air dried to constant weight. The suspension was accomplished by mechanical means (2) consisting of a glass tube and pestle ground to fit.

A suspension consisting of 1 mg. of dried tubercle bacilli per cubic centimeter was first prepared by grinding the bacilli in the mechanical grinder and gradually diluting with physiological saline solution. Then 0.1 cc. of this suspension was ground in a second grinder for about three minutes and diluted to 10 cc. with physiological saline solution. The final dilution was then made from this suspension.

Since none of the drugs studied heretofore has been totally effective in controlling experimental tuberculosis, it was thought that the use of partially immunized animals might prove to be a more satisfactory tool for the comparative study of these compounds. With this in mind, the above immunizing and infecting doses of tubercle bacilli were selected to obtain this intermediate state of immunization. In this we were effectively

[1] From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

[2] Present address: Medical Security Clinic, Seattle, Washington.

guided by the investigations on the quantitative aspects of immunization by Corper and Cohn (3)[3] for, as indicated by the tabulated data, while the average postmortem rating of the controls (group A) is 81 that of the immunized controls (group C) is 47.

Each pig in the immunized group C and D was inoculated subcutaneously in the right flank with 0.5 cc. of the suspension containing 0.0005 mg. of Corper's avirulent human strain tubercle bacilli. One month later each pig in all of the groups A, B, C and D received subcutaneously in the left inguinal region 0.2 cc. of the suspension containing 0.0001 mg. of Corper's strain H4008B.

Drug therapy: A drug to meet the requirements for clinical application must have an order of effectiveness over that of any assisting or competing immune reaction and must decisively control the progress of the disease regardless of the immune factors. Since none of the compounds heretofore studied can qualify on this basis, the choice of diaminodiphenylsulfone was made because this compound was shown to be the most effective of the drugs heretofore used for the control of guinea pig tuberculosis (4, 5), both from the standpoint of degree of involvement and of survival time.

Treatment was started in groups B and D three days after infection and was continued until the experiment was terminated two months later. The drug was administered by mixing it with chopped green vegetables in sufficient quantity so that each pig received 0.1 g. of the sulfone daily. The addition of 40 per cent sucrose syrup made this mixture more acceptable to the guinea pigs. For purposes of control each animal in the two control groups, A and C, received the same quantity of chopped vegetables and sucrose syrup daily. Feldman *et al.* (6) have successfully used a similar technique in administering drugs in their experiments; and in previous work we have likewise consistently obtained uniform results.

COMPLICATIONS

During the course of these experiments, but within three weeks after the injection of virulent tubercle bacilli, 5 animals died of streptococcus pneumonia. These animals exhibited no gross evidence of tuberculosis.

ESTIMATION OF RESULTS

After two months of daily treatment the animals were sacrificed and the amount of gross involvement was estimated. To accomplish this a sum of 100 was set for maximum involvement, and the individual organs were assigned the following numbers to indicate the maximum gross involvement in that organ:

Lymph nodes	8
Spleen	24
Liver	28
Lungs	40

In the event the lungs were clear and the hilum nodes were enlarged a value of 5 or 10, depending on the degree of enlargement, was added to the rating.

The basis of selecting these numbers is arbitrary, but is nevertheless based on the hypothesis that the organs which are most readily involved should be given lower values. Also, since each number is divisible by 4, the common procedure

[3] The authors wish to express their gratitude to Drs. Corper and Cohn for providing them with cultures H4008B and their human avirulent vaccination strain.

of designating the amount of involvement of each organ by +, ++, +++, ++++ is readily transferred into this system of evaluation. The sum of the values, thus prorated, is the *postmortem rating* of the animal.

The final results were as follows:

Group	*Pathological rating*
A	81; infected
B	25; infected and drug
C	47; immunized and infected
D	25; immunized and infected and drug

It should be noted that immunization alone reduced the pathological rating from 81 to 47. However, the drug reduced the rating to 25 in the unimmunized (B) as well as the immunized (D) group. Thus the drug overshadowed in effectiveness the immunization to such an extent that no additive benefit was obtained.

DISCUSSION

These results are at variance with those obtained by Steenken, Heise and Wolinsky (1) in which it was found that the combined effects of promin and immunization were greater than that of promin alone. These differences are perhaps only quantitative, for the immunization may have been so thoroughly accomplished that this would have overshadowed the action of any other therapy. Since there were no concurrent immunized controls in their work to indicate how completely the immunization alone would have inhibited the progress of the disease, there are no immediate data available to determine this factor. Extrapolation, however, from a previous work of Steenken and Gardner (7) would indicate that their immunizing procedure alone does not give this great effect. Therefore, on this basis, an additive effect could be assumed.

Under the conditions of our experiments it is evident that previous immunization has not increased the effectiveness of the drug. Since significant immunization was produced (group C), this opens the question of whether there is some inherent antagonism between immunization and drug action. This question is of interest in clinical tuberculosis because we may in the future frequently be dealing with patients partially immunized by an old primary infection who have become reinfected and are considered for chemotherapy. A study of the intereffects of immunization and chemotherapy is therefore desirable.

The difference between our results and those of Steenken *et al.* (1) needs no reconciliation because neither the same drug nor immunization procedure was used, nor was the duration of the experiment the same. It is evident, however, that it is unsafe to assume that the use of immunization and drugs in tuberculous animals will have an additive effect. We feel also that, before the use of immunized animals becomes acceptable for chemotherapeutic studies, standard procedures should be developed.

CONCLUSIONS

1. Controlled immunization produced moderate inhibition of the tuberculosis process in guinea pigs.

2. P,p'-diaminodiphenylsulfone was more effective than immunization in the inhibition of the tuberculosis process.

3. The combined action of immunization and diaminodiphenylsulfone was no more effective than the drug alone. There was no significant difference between immunized and nonimmunized tuberculous guinea pigs when treated for two months with p,p'-diaminodiphenylsulfone.

CONCLUSIONES

1. La inmunización fiscalizada obtuvo moderada inhibición del proceso tuberculoso en el cobayo.

2. La p,p'-diaminodifenilsulfona resultó más eficaz que la inmunización para inhibir el proceso tuberculoso.

3. La combinación de la inmunización y la diaminodifenilsulfona no mostró mayor eficacia que la droga sola, sin que se observara diferencia significativa entre los cobayos tuberculosos inmunizados y los no inmunizados cuando se les trató por espacio de dos meses con p,p'-diaminodifenilsulfona.

REFERENCES

(1) Steenken, W. Jr., Heise, F. H., and Wolinsky, E: Treatment of experimental tuberculosis in the vaccinated and nonvaccinated guinea pig with promin, Am. Rev. Tuberc., 1943, *48*, 453.

(2) Corper, H. J., and Cohn, M. L.: A mechanical device for preparing fine suspensions of tubercle bacilli and other organisms, J. Lab. & Clin. Med., 1936, *21*, 428.

(3) Corper, H. J., and Cohn, M. L.: Quantitative aspects of specific tuberculoimmunity, Am. Rev. Tuberc., 1943, *47*, 509.

(4) Smith, M. I., Emmart, E. W., and Stohlman, E. F: The action of some derivatives of 4-4'diamondiphenylsulfone in experimental tuberculosis, Am. Rev. Tuberc., 1943, *48*, 32.

(5) Sher, B. C., and Kloech, J. M.: Unpublished work.

(6) Feldman, W. H., Hindshaw, H. C., and Moses, H. E.: Promin in experimental tuberculosis: Sodium p,p'-diaminodiphenylsulphone-N,N'-dextrose sulfonate, Am. Rev. Tuberc., 1942, *45*, 303.

(7) Steenken, W., Jr., and Garnder, L. U.: Vaccinating properties of avirulent dissociates of five different strains of tubercle bacilli, Yale J. Biol. & Med., 1943, *15*, 193.

DERIVATIVES OF P,P'-DIAMINODIPHENYLSULFONE AND SULFANILAMIDE IN EXPERIMENTAL TUBERCULOSIS[1]

HENRY C. SWEANY, BEN C. SHER AND JOHN M. KLOECK[2]

In extending our previous studies on some chemical factors influencing the growth of tubercle bacilli (1, 2), the relative tuberculostatic values of a number of sulfanilamide and diaminodiphenylsulfone derivatives were determined (3). Some of these compounds were chosen because they were known to be highly effective in the treatment of other bacterial infections, while the others were tested on the basis of their similarity in chemical structure.

Obviously the use of relative tuberculostatic values for screening out the non-effective compounds presupposes that the compounds are sufficiently soluble in the medium to give an effective concentration and that some compounds which might have proved to be effective by *in vivo* tests may be prematurely ruled out. But since it is impractical to establish *in vivo* ratings on every compound made available for this purpose, a method, even with limitations, is needed. On this basis then it seemed logical, until a better correlation between *in vitro* and *in vivo* ratings is obtained, to select the following tuberculostatic compounds from table 1 for exploratory studies against experimental tuberculosis: 1021, 1048, 1114, 1140, 1142, 1147, promin and sulfapyridine.

METHODS

Animals and controls: These studies consist of five groups of experiments in which a total of 113 guinea pigs were used. Each pig was inoculated in the right groin with 0.0001 mg. virulent bovine tubercle bacilli (Ravenel). The grouping, subsequent treatment, dosage and other data are as indicated below, under Results.

Administration of drugs: The chronological order in which each drug was studied and the number of animals used in each experiment were determined by the availability of each compound. For intraperitoneal administration each drug was dissolved in a 5 or 10 per cent aqueous solution and injected into the left flank. For oral treatment each drug was dissolved or suspended in sugar solution and fed with a Pasteur pipette.

Estimation of results: The gross postmortem rating of each animal was determined by adding the values prorated for each organ involved according to the method described in the preceding paper by Sher and Kloeck (4). The values obtained ranged from 0 to 100

RESULTS

Results of groups A and B: Compound 1021 was the first drug obtained in large enough quantities for the preliminary experiments (group A, table 2). Eighteen days later compounds 1048 and 1114 were available and the second group was started (group B). From this point these two groups are considered together.

During the course of treatment palpable nodes appeared at the site of inoc-

[1] From the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium, Chicago, Illinois.

[2] Present address: Medical Security Clinic, Seattle, Washington.

ulation in all animals, except in those that received compound 1048 within two days after they were infected. To determine the significance of this, most of the animals were sacrificed.

It was found from the data thus obtained that compound 1048 retarded the tuberculous process to an extent that varied with the experimental conditions. In one experiment, which may be characterized as our "Optimum Experiment" because optimum conditions apparently prevailed to produce these excellent results, the postmortem rating was zero. There was no gross or microscopic evidence of tuberculosis and the results were negative upon reinoculation of the macerated spleens. Treatment started in this instance two days after infection and consisted of 37 daily doses, 16 of which were 100 mg. each followed by 21 doses of 50 mg. each (total, 2.65 g.). In a parallel experiment, in which the animals were given one-half as much drug, the retarding effect was less, for the average postmortem rating was 43.

In an additional experiment in which treatment was initiated eighteen days after infection, the average postmortem rating was 57. This is somewhat higher than the rating of 48 for the control animals of this group which were sacrificed at twenty-six days, and it is significantly lower than the rating of 87 for the comparable untreated controls sacrificed along with the treated animals at forty-five days. Although larger doses of drug were administered (a total of 3.65 g. during twenty-three days of treatment), the action of the drug was less spectacular; the disease was well established when treatment started. However, there was a significant retarding effect.

The duration of the foregoing experiments was forty-five days.

Two experiments were included in this group in which treatment was delayed three and four weeks, respectively. These experiments were prolonged up to one hundred days to determine the effect of longer treatment (6.6 g. and 8.25 g. of 1048 were the respective total amounts of drug administered). The larger doses were more effective, even though treatment was delayed for the longer period. The respective ratings were 95 and 72 for these experiments.

Compound 1021 was less effective than 1048 when given in the same amounts. In no instance was any animal free of tuberculosis and the average postmortem rating was higher in each comparable experiment.

Compound 1114 was less effective than 1021 or 1048.

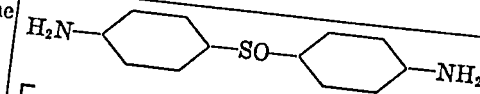
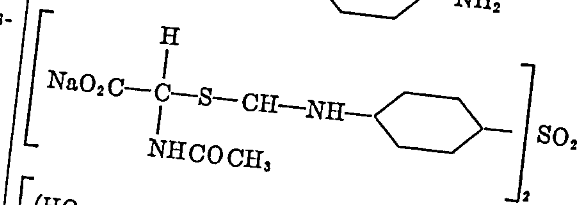
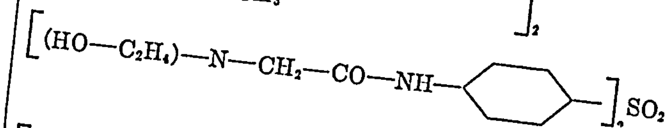
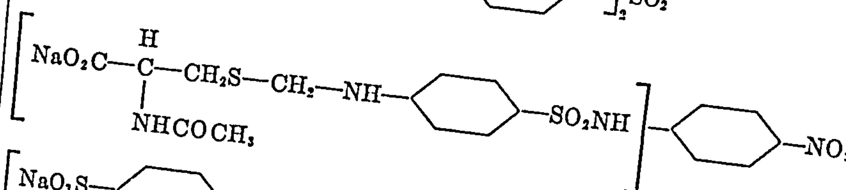
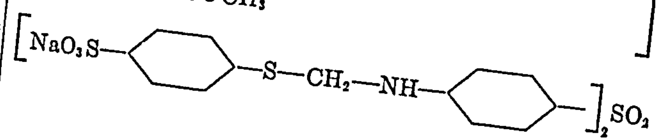
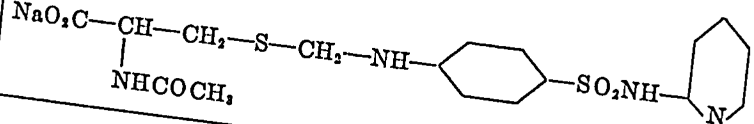
Results of groups C and D: These groups of experiments were performed to determine the value of oral administration of compound 1048, and also to collect more data when this compound is given intraperitoneally. Compounds 1140, 1142, 1147 and sulfapyridine were also studied.

The excellent results obtained in our "Optimum Experiment" were not reproduced in this group, for in each experiment in groups C and D there was some involvement. Palpable nodes were detected at the site of injection before twenty-five days, and at autopsy there was at least generalized involvement of the lymph nodes in each animal.

The average postmortem ratings in these groups indicate again that compound 1048 is the most effective.

TABLE 1

*Relative order of tuberculostatic effectiveness**

COMPOUND	CHEMICAL NAME	CHEMICAL FORMULA	MG. PER CENT INHIBITED	MG. PER CENT RETARDED
Sulfone	4,4′-Diaminodiphenylsulfone		0.8	0.16
1048	Disodium salt of *N*,*N*′-Bis-(β-carboxy-β-acetamido-ethylthiamethyl)-4,4′-diaminodiphenylsulfone		0.8	0.16
1208	*N*,*N*′-Bis-(di-β-hydroxy-ethylaminoaceto)-4,4′-diamonodiphenylsulfone		4.0	0.16
1147	*N*-p-Nitrophenyl-*N*-(β-Carboxy-acetamidoethylthiamethyl)sulfanilamide		0.8	0.8
1021	Disodium salt of *N*,*N*′-Bis-(4 sulfaphenylthiamethyl)-4,4′-diaminodiphenyl-sulfone		4.0	0.8
1140	*N*(β-Carboxy-β-acetamido-ethythiamethyl) sulfapy-ridine		4.0	0.8

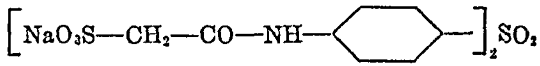
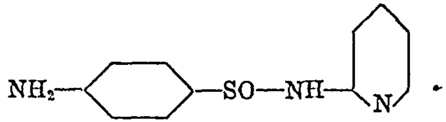
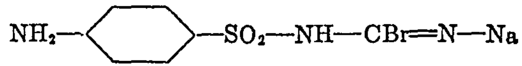
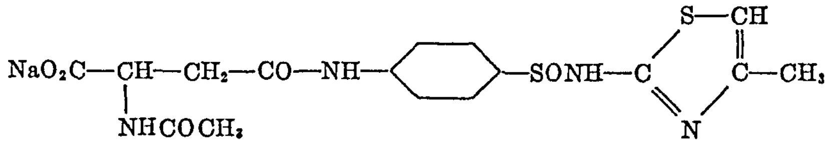
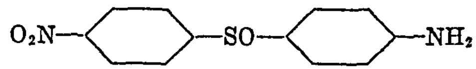
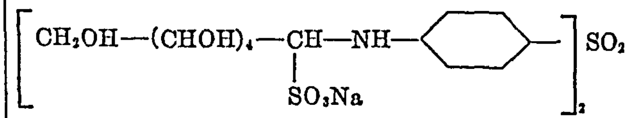
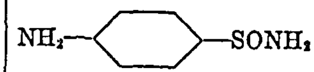
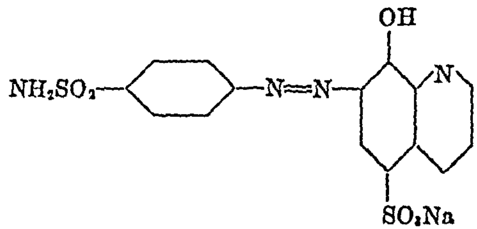
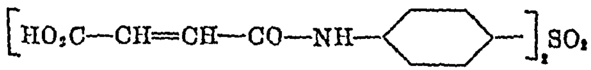
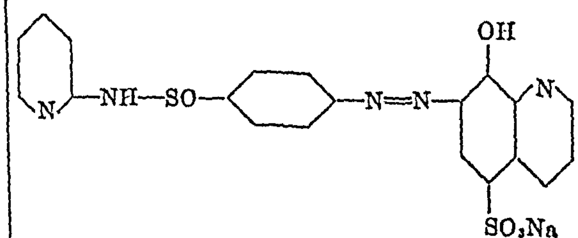
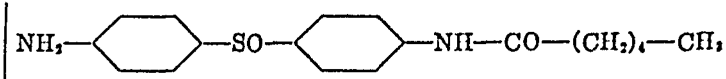
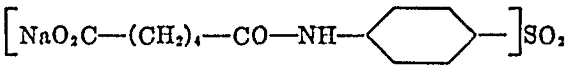
1209	Disodium salt of *N,N'*Di-(sulfaceto)-4,4'-diaminodiphenylsulfone		4.0	0.8
Sulfapyridine	Sulfapyridine		4.0	0.8
1114	Sodium N^1-Bromocyanosulfanilamide		4.0	0.8
11142	*N*(β-Carboxy-β-acetamidoethylthiamethyl)sulfamethylthiazole		4.0	0.8
4-Amino-4'-*nitrodi*-phenylsulfone	4-Amino-4'-nitrodiphenyl-*sulfone*		4.0	4.0
Promin	Sodium P,P'-Diaminodiphenylsulfone-*N,N'*Di-dextrosesulfonate		20.0	4.0
Sulfanilamide	Sulfanilamide		20.0	4.0
1011	Sodium salt of N-(Carboxymethylthiamethyl)-4,4'-diaminodiphenylsulfone		20.0	4.0

TABLE 1—*Continued*

COMPOUND	CHEMICAL NAME	CHEMICAL FORMULA	MG. PER CENT IN-HIBITED	MG. PER CENT RE-TARDED
4-Nitro-4'-caproamido-diphenyl-sulfone	4-Nitro-4'-caproamidodi-phenylsulfone		20.0	20.0
1161	5 Sulfa-7-(p sulfamylben-zeneazo)-8-hydroxy quinoline		20.0	20.0
1019	N,N'Dimaleyl-4,4'-diamino-diphenylsulfone		20.0	20.0
1162	5 Sulfa-7-(p-N pyridylsul-famylbenzeneazo)-8-hydroxy quinoline		>20.0	20.0

1207	4-Amino-4′-caproamidodiphenylsulfone		>20.0	>20.0
	Disodium salt of N,N′-Diglutaryl-4,4′diaminodiphenylsulfone		>20.0	>20.0

* *Note:* The relative effectiveness of each substance was determined in Longs synthetic medium to which 2 per cent agar had been added (1). The first and highest concentration, 20 mg. per cent, was prepared by weighing between 5 and 10 mg. of the compound on a microbalance, to the nearest 0.1 mg. This was then incorporated in 5 ml. of medium for each mg. of substance. The three subsequent dilutions were made by adding 4 ml. of medium to each ml. of the previous concentration. In the event a compound was not sufficiently soluble, it was dissolved in 1 or 2 ml. of alcohol and then dispersed in the proper volume of medium.

Slants were prepared in triplicate for each concentration with controls in duplicate. These were allowed to gel in trays especially designed (3) to facilitate the necessary operations such as the serial dilution, inoculation, inspection and stacking of the culture tubes in the incubator.

Large enough batches of medium were prepared so that any unknown factors that might creep in would be uniform throughout the experiment. The series of dilutions were all prepared in one day, and on the day before they were inoculated. The inoculating suspension (B599, a rapidly growing bovine strain) was prepared by the use of a mechanical device from a young culture, and a uniform quantity applied to each slant. The inoculation of the series, like its preparation, was accomplished at one sitting.

Whenever it was desirable to compare one series with another, extrapolation was accomplished by including two or more previously evaluated compounds in the new series.

Results of group E: During the course of this work excellent results were obtained with promin (5) by Feldman *et al.* Consequently, the experiments in

TABLE 2

Summary of experimental data

GROUP	COMPOUND	DURATION OF EXPERIMENT	TOTAL AMOUNT OF DRUG ADMINISTERED	AVERAGE POSTMORTEM RATING	AGE OF INFECTING CULTURE
		days	*grams*		*weeks*
A	1021	59	3.5	42	4
	1021	59	1.75	49	
	1021	59	5.05 (a)	62	
	Control	59		100	
B	1048	45	2.65	0	11
	1048	45	1.33	43	
	1048	45	3.65 (a)	57	
	1048	100	6.60 (a)	95	
	1048	100	8.25 (b)	72	
	Control	45		87	
	Control	26		48	
	1114	42	3.5	62	
	1114	42	1.75	65	
	1114	40	3.15 (c)	77	
C	1048	51	5.2	48	?
	1048	57	0.7	90	
	1048	59	4.7	56	
	1048	59	5.3	48	
	1048	57	7.6 (c)	50	
	Sulfapyridine	59	7.3	93	
	1140	54	9.4	68	
	1142	54	9.4	78	
	Controls	59		88	
D	1048	66	14.	52	5
	1147	66	3.4	100	
	Controls	64		100	
E	1048	71	5.75	41	3
	Promin	71	6.6	45	
	1048	30	5.75	4	
	Promin	30	6.6	10	

(a) Treatment was delayed three weeks.
(b) Treatment was delayed four weeks.
(c) Treatment was delayed two weeks.

group E were performed to compare the action of promin with 1048, and also to determine the action of promin under the conditions imposed in our experiments.

When 22 daily doses of 250 to 300 mg. of each of these drugs were given intraperitoneally there was less tuburculosis than in untreated animals, although more

tuberculosis appeared than was found by other investigators. Most of the animals were sacrificed forty-six days after the last dose was administered; the average postmortem ratings were 41 for compound 1048, 45 for promin and 97 for comparable controls. The remainder of the animals were sacrificed only five days after the last dose was given, and the ratings were 4 and 10, respectively. As found in group B, when the treatment was discontinued the disease continued to progress.

DISCUSSION

Compounds 1048, 1021 and promin are sulfone derivatives and are the only effective drugs in this series. Of these, 1048 gave the best results. The other compounds are sulfanilamide derivatives, and are not effective. This is in agreement with observations by other investigators (5, 6, 7) who found that the sulfones are effective by tests *in vivo*, and the sulfanilamide derivatives are not, even though they received relatively high *in vitro* ratings.

Because of the excellent results obtained in our so-called "Optimum Experiment" with compound 1048, this drug was studied more intensively than the other compounds. However in none of the subsequent experiments were these results duplicated. The explanation of our inability to reproduce these results is based on the following considerations.

Within group B the use of smaller doses of drug resulted in a poorer showing, for when the dosage was reduced by one-half the tuberculous process was only partially checked. It would have been of interest if we were enabled to extend and prolong this "Optimum Experiment" with and without continued treatment to determine if positive findings would have developed. This was not done, except in some experiments outside of group B, and from these we are inclined to believe that tuberculosis would have developed.

The extension of time factors also caused a poorer showing, for in those animals in which treatment was delayed eighteen days tuberculosis was well established before treatment was initiated. The disease advanced somewhat under treatment, but not as rapidly as in untreated comparable controls.

By prolonging these experiments up to one hundred days with continued treatment even higher index values were obtained. Consequently, once the infection was well established, the disease progressed even under treatment. It is noteworthy that the larger doses more effectively retarded this process.

Experiments are in progress to ascertain whether signs of regression would appear if these experiments were prolonged indefinitely.

The poorer results obtained in experiments other than in group B may have been caused by inherent differences in the subcultures used, for in some of these subsequent experiments the conditions of dosage and time are comparable to those of the more successful experiments.

The subculture used for the preparation of the inoculum for group B was grown for eleven weeks, while those for the other groups were grown from three to five weeks. It is conceivable, then, that the older culture had fewer live bacilli and had other characteristics that caused it to be less virulent than the

younger growth. Therefore, in group B it may be assumed that the drug had a less vigorous infection to combat, and under the optimum conditions the tuberculous process was completely inhibited. To support this view, it may be recalled that in group B, when treatment was started within two days, no palpable nodes appeared at the site of inoculation even at forty-five days, while in all the other groups in which younger cultures were used, nodes were detected before twenty-five days. This earlier appearance of demonstrable evidence of tuberculosis in otherwise comparably treated animals is a manifestation of the greater reactivity of these younger cultures.

Other factors may be inherent in the subculture which concern themselves with the activity of the inoculum for, even with age of the culture and other factors standardized, the virulence of the cultures varied. This is attested to not only in our own experience, but also in that of other investigators (8, 9) in which one group of control animals survived for about two to three months, while from presumably identical cultures, similar groups of animals lived for about six to seven months.

A greater amount of tuberculosis appeared in our treated animals than was reported by other investigators (5, 8). This is true not only of the present series in which the Ravenel strain was used, but also when we used a subculture of the H37RV used by Feldman and his coworkers and kindly sent to us by Feldman. It was therefore of interest to determine how much tuberculosis would result when promin, a substance for which the effectiveness had been determined, was submitted to our tests. More involvement was found in our tests than was obtained by other investigators. It is our feeling that these results may be due to our selection of the right groin as the site of inoculation, while other workers selected the sternal region. In the groin or inguinal region, the lymphatics readily become involved. Once this has occurred nodes are formed which presumably serve as a reservoir of tubercle bacilli. From these there is a constant source of infection which has proved to be too great to be overcome by the drugs heretofore studied.

To conclude, the authors wish to stress that these experiments were exploratory and none was sufficiently extensive to determine whether these or similar drugs are suitable for clinical tests. However, the data accumulated have served as a guide for our subsequent studies soon to be submitted.

SUMMARY

1. Three p,p′-diaminodiphenylsulfone derivatives and five sulfanilamide derivatives were selected from a series of *in vitro* tests for further tests in experimental tuberculosis.

2. Each of the p,p′-diaminodiphenylsulfone derivatives effectively retarded the tuberculous process in guinea pigs.

3. The sulfanilamide derivatives were noneffective although each received a high *in vitro* rating.

4. Compound 1048 was the most effective by tests *in vivo*.

5. The amount of tuberculous involvement varied between experiments and

differed from that found by other observers. This is due to the characteristics of the inoculum and other factors resulting from the conditions imposed in our experiments.

SUMARIO

1. Tres derivados de la p,p′-diaminodifenilsulfona y cinco derivados de la sulfanilamida fueron seleccionados de una serie de ensayos *in vitro* para nuevos ensayos en la tuberculosis experimental.

2. Todos los derivados de la p,p′-diaminodifenilsulfona retardaron eficazmente el proceso tuberculoso en el cobayo.

3. Los derivados de las sulfanilamidas se mostraron ineficaces aunque todos habían recibido una clasificación alta *in vitro*.

4. En los ensayos *in vivo* el compuesto 1048 resultó ser el más eficaz.

5. La magnitud de la invasión tuberculosa varió en los experimentos, discrepando de lo descubierto por otros observadores, lo cual se debe a las características del inóculo y a otros factores relacionados con las condiciones impuestas en estos experimentos.

Professor M. S. Kharasch and Dr. Otto Reinmuth, of the University of Chicago, provided us with most of the compounds studied in this paper, and gave us their excellent coöperation. Eli Lilly and Company provided us with a number of compounds, especially Kharasch Compound 1048 in large quantities. Parke, Davis & Company provided the promin. To these we wish to express our gratitude.

REFERENCES

(1) Sher, B. C., and Sweany, H. C.: Chemical factors influencing the growth of tubercle bacilli: I. Metal catalysts, J. Bact., 1939, *37*, 377.

(2) Sher, B. C., and Sweany, H. C.: Chemical factors influencing the growth of tubercle bacilli: II. Organic reagents, *J. Bact.*, 1939, *38*, 411.

(3) Sher, B. C.: Chemical factors influencing the growth of tubercle bacilli: III. Chemotherapeutic and other reagents, unpublished work (to be submitted for publication).

(4) Sher, B. C., and Kloeck, J. M.: The combined action of p,p′-diaminodiphenylsulfone and immunization in experimental tuberculosis, Am. Rev. Tuberc., 1946, *65*, 239.

(5) Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: Effect of promin (sodium salt of p,p′-diaminodiphenylsulfone-N,N′-dextrose sulfonate) on experimental tuberculosis: A preliminary report, Proc. Staff Meet. Mayo Clin., 1940, *15*, 695.

(6) Callomon, Fritz F. T.: New derivatives of diaminodiphenylsulfone: Their therapeutic effect in experimental tuberculosis of guinea pigs, Am. Rev. Tuberc., 1943, *47*, 105.

(7) Medlar, E. M., and Sasano, K. T.: Promin in experimental tuberculosis in the guinea pig, Am. Rev. Tuberc., 1943, *47*, 618.

(8) Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: Promin in experimental tuberculosis: Sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate, Am. Rev. Tuberc., 1942, *45*, 303.

(9) Feldman, W. H., Mann, F. C., and Hinshaw, H. C.: Promin in experimental tuberculosis: Observations on tuberculous guinea pigs before and after treatment with sodium p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate (promin), Am. Rev. Tuberc., 1942, *46*, 187.

TUBERCLE BACILLI IN THE METABOLIC APPARATUS[1]

M. G. STEMMERMANN[2] AND ARTHUR STERN

Notwithstanding our sure knowledge of its virulence, viability and physical characteristics, the itinerary of the tubercle bacillus from one pulmonary depot to another has never been completely established. That its commonest route is a direct mouth to mouth one, via infected oral discharges, has been generally accepted on the basis of many experimental studies and of clinical experience. That its passage may be affected by such passive vectors as dust, clothing, toys, books and eating utensils has been accepted more often by inference than by experimental evidence. In fact, experimental work indicates the rarity of mechanical vectors in the dissemination of tubercle bacilli.

Bogen and Dunn (1) found but few places at Olive View Sanatorium in which exposed Petri dishes yielded cultures of tubercle bacilli. Jacobs and Petroff (2) failed to recover tubercle bacilli from the books or clothing of patients at Sea View Hospital, although, for the purposes of the experiment, the patients were urged to be as careless as possible while coughing and expectorating.

Among the vectors that it has been assumed are factors in the dissemination of the tubercle bacillus is the respiratory apparatus, particularly the instrument used in the determination of the metabolic rate. Large sanatoria often have two machines for the use of "positive" and "negative" patients, respectively. Where but one apparatus is available its use is often restricted to those patients whose pulmonary discharges are free of tubercle bacilli. The following experiments were designed to determine whether or not such organisms could be isolated from the respiratory apparatus, in order that its rôle as a vector in the dissemination of tuberculosis might be evaluated.

MATERIAL AND METHODS

Fourteen patients were selected for the experiment, all of whom had far advanced pulmonary tuberculosis with two or more excavations. The combined diameters of the cavities equalled from approximately 5 cm. per patient to more than 10 cm. The sputa in each case consistently contained large numbers of tubercle bacilli which were estimated to range from Gaffky five to Gaffky ten.

For the purposes of the experiment, basal conditions were obviously not required. Except as noted below, the tests were otherwise performed for ten minutes in the conventional fashion for determining the metabolic rate with the Sanborn waterless apparatus. From figure 1 it can be seen that expired air is filtered through the soda lime, enters the oxygen filled spirometer, and is rebreathed through tube B, carbon dioxide being absorbed by the soda lime at the base of the instrument.

After two to four minutes' quiet respiration, each patient was asked for his greatest possible expiration following the deepest possible inspiration (vital

[1] From the Medical Service of Dr. G. E. Gwinn, Pinecrest Sanitarium, Beckley, West Virginia.

[2] Medical Director, Owen Clinic, Huntington, West Virginia.

capacity). The expiration was usually terminated prematurely by a cough which the patient was urged not to suppress. In the few cases in which forced respiration failed to elicit coughing after two or three trials, the patients were requested to cough into the machine at the end of the ten-minute breathing period.

Before the patient was disconnected from the apparatus, the outlet valve was closed. The outlet end of the metal "U" was then inverted into a sterile flask, the outlet valve opened, and the remaining gases in the spirometer were flushed out several times with air. Both connecting rubber tubes and the metal "U" were then flushed with sterile saline, the washings being collected in the same flask, about 300 cc. of saline being used in each case.

The washings thus obtained were centrifuged and the sediment, which contained considerable debris from the rubber tubing, was divided into two parts.

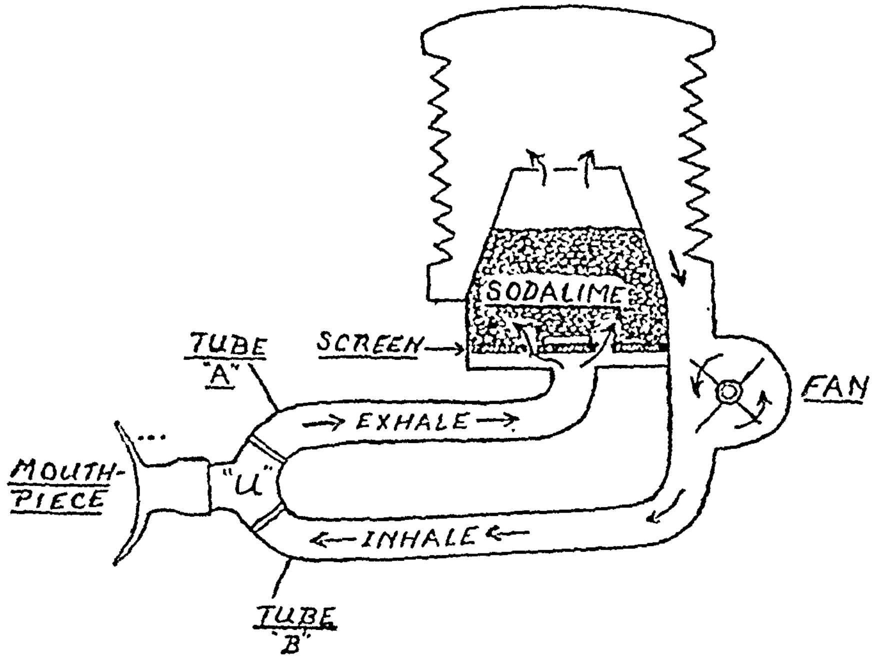


FIG. 1. Metabolic respiratory apparatus

Tube 1 was concentrated with 4 per cent sodium hydroxide and neutralized with 10 per cent hydrochloric acid. The specimen was again centrifuged and the sediment planted on Hohn's medium. Tube 2 was treated in the same manner as tube 1, except that 5 per cent oxalic acid was used for concentrating, the sediment washed with 0.9 per cent sodium chloride and planted on Petragnani's medium. Smears of the sediment were examined directly for tubercle bacilli in both instances. The cultures were examined weekly for two months for growth of tubercle bacilli.

RESULTS AND DISCUSSION

Neither smears nor cultures from 14 washings of the metabolic respiratory apparatus following its use by actively infected tuberculous patients were pos-

itive for tubercle bacilli. Obviously these persons, although they may not have been breathing tubercle bacilli into the spirometer, were certainly coughing bacillary laden particles into the apparatus. That we could not recover these organisms was due to either one or both of two factors.

First, the bacilli may have been too few in number in the air and saline washed portions of the apparatus to be demonstrable by our methods. If this were true, the bacteria must indeed have been few, since we have used similar methods of washing with positive results in testing the bacteriological cleanliness of gastric tubes following their use by tuberculous patients.

Second, and more probably, the organisms may have been filtered out by the soda lime at the bottom of the machine and have therefore been irreclaimable. It would appear, then, that this type of respiratory apparatus can rarely, if ever, act as a vector in the spread of pulmonary tuberculosis. This would also be true of the Benedict-Roth apparatus in which the expired air likewise passes first through soda lime before entering the remainder of the spirometer and the intake tubing.

CONCLUSIONS

In order to determine whether or not the basal metabolism machine may act as a mechanical vector in the dissemination of pulmonary tuberculosis, this instrument was tested for the presence of tubercle bacilli. After each of 14 patients with massively positive sputum had breathed and coughed into the machine for ten minutes, the remaining gases were flushed out with air and the connecting rubber hoses were irrigated with saline. In not a single instance could tubercle bacilli be recovered from the washings, indicating that even after its continued use by highly "positive" patients the basal metabolism machine is not a likely factor in the spread of pulmonary tuberculosis.

CONCLUSIONES

A fin de determinar si los aparatos usados para estudiar el metabolismo basal pueden actuar como vectores mecánicos en la difusión de la tuberculosis pulmonar, se comprobó en uno de dichos instrumentos la presencia de bacilos tuberculosos. Después que cada uno de 14 enfermos con esputo intensamente positivo había respirado y tosido en el aparato durante diez minutos, se expulsaron los gases restantes con aire y se lavaron con solución salina los tubos de caucho conectantes. Ni en un solo caso pudieron encontrarse bacilos tuberculosos en los lavados, lo cual indica que, aun después de su continuo empleo por enfermos altamente "positivos", no es probable que el aparato del metabolismo basal constituya un factor en la propagación de la tuberculosis pulmonar.

REFERENCES

(1) Bogen, E., and Dunn, W.: Tubercle bacilli in air and dust, Am. Rev. Tuberc., 1941, 43, 435.
(2) Jacobs, M. A., and Petroff, S. A.: Etiological studies of tuberculosis. 1. The occurrence of tubercle bacilli on garments and books handled by patients with open tuberculosis, Quart. Bull. Sea View Hosp., 1941, 7, 33.

BOOKS

Max Pinner: *Pulmonary Tuberculosis in the Adult. Its Fundamental Aspects. Pp. xiii + 579, with 59 figures, and 4 graphs, Charles C Thomas, Publisher, 301–327 East Lawrence Avenue, Springfield, Illinois, U. S. A., 1945, fabrikoid, $7.50.*

By J. BURNS AMBERSON

Max Pinner set for himself a clear and specific purpose in writing this book which is "... not to impart knowledge but to create understanding, to form rational and consistent attitudes and approaches to the problem as a whole, to provide the basically necessary foundations on which ... the practical work should proceed." It is a bold and worthy purpose which few could undertake to fulfill, but one which immediately engages the interest of the student of pulmonary tuberculosis. In so setting his course the author avoided the onus of assembling and presenting the minutiae of factual knowledge, freed himself to select those facts which he considers pertinent and significant, and allowed himself wide scope for integration and interpretation. In short, he eschewed the rôle of encyclopedist to take that of expositor and philosopher. No one may fairly essay the rôle until years of experience, study and contemplation have seasoned him with such wisdom as Pinner now possesses.

The selected data are from original sources and include a faithful, adequate and accurate account of the thinking of such students as Koch, Ranke and Krause. The author succeeds in distilling the essence of significant conceptions, analyzing it in an interesting and often very penetrating way, and then blending the material which passes the analytic test into new, modified or amplified conceptions according to his own reasoning and judgment. In doing so he keeps a fine balance of objectivity, avoids bias and special pleading, and maintains a true perspective of the relative meaning of his own researches. At the end of each chapter and finally at the end of the book are added a selection of references (some treated at length in the text) with concise and informative annotations.

In revealing, analyzing and formulating many basic principles, the author's approach is broad and versatile; he brings to bear known facts from all sides, experimental, bacteriological, pathological, roentgenological and clinical. Thus, in explaining the exudative reaction to tuberculous infection in the lungs, he discusses the pathological peculiarities resembling those of nonspecific pneumonia, stresses the practical importance of differentiation and discusses the clinical implications. Here one may doubt whether exudative lesions completely resolve as often as Pinner seems to think, may lay more emphasis on the time required for their stabilization and durable arrest, and may prefer sometimes to possess himself in patience longer before inducing pneumothorax for one which starts to break down and excavate. But these are shades of opinion which would be permitted anyone and which in no way detract from Pinner's insistence on the invariable instability of such lesions at inception, their potentialities for harm, especially in young people, and the need for prompt and careful treatment.

An informative epitome is given of the properties of the tubercle bacillus, of its chemical nature, and of the limitations of interpreting biological reactions to chemical fractions in terms of the natural disease. The problems of immunity and allergy, which in most books seem to defy elucidation, are presented with admirable clarity. While obscure corners are indicated as such, sound principles are singled out for their fundamental importance; for example, ". . . in not a single experiment has it been possible to increase the innate resistance of an animal without producing tuberculous tissue in it." (p. 97) How futile experimentation on immunity would be if this were ignored! Likewise, how cogent for the clinician is the conception, "Phthisis is in essence a Koch phenomenon in the lung." (p. 125)

Not every opportunity is taken to define conditions in such a sharp and arresting way. Pinner, for instance, follows the usual practice of describing the meaning of the tuberculin reaction as "infection" but not necessarily "disease." It is not just purism to insist that infection is the process of implanting the bacillus into the body and that this alone does not sensitize the tissues to tuberculin; only after the lesion appears does this happen. It would be better for understanding, therefore, if the current aphorisms anent the tuberculin reaction could be modified somewhat as follows: *A reaction means tubercle (or even tuberculosis) but not necessarily progressive tuberculosis.* Other voices have so spoken in the past, but they were too small and still. Nevertheless, this objection against form of expression is quite subordinate to acknowledgment of the excellence of the discussion of tuberculin and its uses.

The chapters on phthisiogenesis and the inception and course of pulmonary tuberculosis are also typically logical, lucid and sound. Some will consider the frequency of hematogenous lesions of the lungs, especially of adults, to be overrated and will contend that the roentgenographic illustrations of some such cases may be interpreted differently, but few will disagree that "epituberculosis" is more of a term (and a poor one at that) than a well defined pathological lesion. Pinner reports some observations of American internists that primary lesions in adults do not behave differently from reinfection lesions, but the recent experience indicates that the former are more unstable and likely to progress.

The discussion of bronchial tuberculosis and its consequences will be most helpful to physicians dealing with tuberculous patients. Much confusion is cleared away especially concerning "atelectasis" which usually is a mistaken diagnosis and turns out to be pneumonia, edema, fibrosis or a combination of these with suppuration.

While the value of the Gaffky scale is severely and deservedly depreciated, the importance of detecting tubercle bacilli in the sputum or proving their absence is properly emphasized in differential diagnosis and in determining the activity of lesions. Leucocyte counts are affirmed to be valuable in differential diagnosis but relatively useless in prognosis as compared with other observations. For the first time in any book of this character, an adequate, up-to-date consideration of the physiological principles of respiration is presented. Treatment, medical and surgical, is discussed, not as to details and techniques, but according

to fundamentals, detailing many of the mechanisms involved. Indeed, selection of treatment is often an easy and logical inference after one grasps and understands what is known about these mechanisms. The reasoning throughout is distinguished by good sense which comes of sound experience. The final chapter on epidemiological principles fills out the picture as the author originally conceived it.

A very commendable feature of the book is the selection and quality of the illustrations. These are obviously chosen to demonstrate specific observations and they are reproduced clearly so as to show what they are supposed to show. They match well with the easily readable printing and the pleasing format.

The purpose of the book is achieved surpassingly well. The receptive neophyte in this field of medicine will be informed and oriented. The experienced physician will certainly be reoriented, will acquire understanding and will be stimulated to pursue through his own efforts the endless quest of better understanding.

RUTH RICE PUFFER: *Familial Susceptibility to Tuberculosis. Its Importance as a Public Health Problem. Pp. x + 106, Cambridge, Massachusetts, Harvard University Press, 1944, cloth, $2.00.*

By DAVID REISNER

The old theme of the "seed" and the "soil" or, in other words, the question as to why certain persons exposed to infection with the tubercle bacillus develop the disease, while others under comparable conditions of exposure fail to do so, remains one of the fundamental problems in the pathogenesis of tuberculosis. This monograph emphasizes the importance of two basic factors in the causation of tuberculosis, namely, exposure to infection and familial susceptibility to the disease. Most of the data included in the book represent the result of intensive epidemiological studies which have been carried on by Doctor Puffer and her coworkers since 1931, as a part of a special project in Williamson County, Tennessee, with the assistance of the International Health Division of the Rockefeller Foundation.

In introductory chapters the author summarizes some of the older and more recent literature dealing with the problem of heredity and tuberculosis and reviews observations on familial susceptibility in diseases other than tuberculosis, such as leprosy, rheumatic fever, poliomyelitis and diabetes. There is also a summary of recent experimental work in animals, pointing to the significance of hereditary factors in susceptibility and resistance to infectious diseases, especially tuberculosis, as well as a review of twin studies carried out on human material.

The greater part of Doctor Puffer's book is devoted to a statistical analysis and interpretation of the epidemiological data of the Williamson County Study. Morbidity and mortality figures in siblings, consorts, parents and children of tuberculous index cases are presented and analyzed, and a good deal of convincing evidence is adduced in favor of familial susceptibility to the disease.

Of particular interest are the data dealing with the controversial question as to frequency of the disease in consorts of persons with tuberculosis. The percentages of consorts with manifest disease were high, especially so for consorts of sputum-positive cases, a finding pointing to the importance of household exposure. However, when the consorts were separated into two categories according to the presence or absence of tuberculosis in members of their own families, such as parents and siblings, the frequency of the disease was found to be significantly higher in consorts with a family history of tuberculosis than in those without such history.

The author presents interesting data relative to tuberculosis mortality of parents of tuberculous index cases. It is shown that the death rates of parents, especially of mothers, have remained excessively high over long periods of time, while the total death rate has shown a marked decline during this period. This is attributed to continued familial aggregation of the disease and it is suggested that the general decline of tuberculosis mortality may be due to a reduction in the proportion of susceptible families.

There are some significant observations on the occurrence of tuberculosis in the children of tuberculous parents. While the attack rates of children of a parent *with* sputum-positive tuberculosis were found to be high in childhood and in young adult life, after the age of 30 the attack rates of children of a parent who had tuberculosis *without* known positive sputum exceeded those of the former age groups. "By 50 years of age approximately the same proportion of both groups of children had developed tuberculosis." Prevalence rates in children of tuberculous parents were practically identical in those removed from home without known exposure, as in those with household exposure to infection, thus suggesting "that children of tuberculous parents are susceptible to the disease."

The concluding chapter contains some specific recommendations concerning control measures, based on the observations of this study. It is emphasized that case-finding activities should be concentrated on the susceptible groups of the population made up of tuberculous families. The recommendation is made to extend the case-finding programs to include observation of household associates of persons with tuberculosis, as well as follow-up of close blood-relatives, such as parents, siblings and children of the tuberculous, irrespective of household exposure. While there would seem to be a good deal of evidence to justify such a program, there may be some question as to how far it could be carried out in practice in view of the constantly shifting population, especially in large urban centres.

Doctor Puffer's monograph should stimulate similar family studies in other parts of the country. It would be of particular value to carry out such studies in areas where tuberculosis is less wide-spread in the total population than is apparently the case in Williamson County, as they might reveal a more distinct separation between susceptible and resistant groups.

This book should be of great interest to all students of tuberculosis, clinicians as well as public health workers and epidemiologists.

Erik Hedvall: *Bovine Tuberculosis in Man. A Clinical Study of Bovine Tuberculosis, Especially Pulmonary Tuberculosis, in the Southernmost Part of Sweden. Acta Medica Scandinavica, Supplementum CXXXV, Mercators Tryckeri, Helsingfors, 1942, pp. 239.*

By J. A. Myers

The first actual isolation of the bovine type of tubercle bacillus from human lesions was accomplished by Ravenel in 1902. These were found in abdominal lesions of a child who had died from tuberculous meningitis. Although the fact was soon established that extrathoracic tuberculous lesions frequently are produced by the bovine type of bacillus, it was long believed that this organism does not cause pulmonary disease in man. In fact, prior to 1922 only 4 such cases had been reported. However, in 1932 among 1,040 cases of pulmonary tuberculosis, Griffith found that 2.3 per cent were due to the bovine type of bacillus. In 1937 he reported a total of 163 such cases in Great Britain. They ranged in age from 7 to 72 years. In 1935 Tobiesen *et al.* described 26 cases of pulmonary tuberculosis due to the bovine type of bacillus in Denmark. Three years later Jensen, of the same country, found this organism in the gastric contents of 5 per cent of 1,774 cases of pulmonary tuberculosis. In Holland, Ruys examined 204 cases of pulmonary tuberculosis and found the bovine type of bacillus in the sputum of 6.4 per cent. Lange in Germany reported 40 cases of pulmonary tuberculosis among stable-boys and milkers, of whom the bovine type of bacillus was responsible for 20 per cent. Thus Doctor Hedvall's present contribution not only confirms the work of others, but also emphasizes the great importance of protecting humans against the bovine type of tubercle bacillus.

In this fine monograph, Hedvall reports in considerable detail 67 cases of tuberculosis in man caused by the bovine type of organism in the Province of Skåne, Sweden. These patients ranged from 3 to 68 years of age. While analyzing the data for this report 27 more cases were diagnosed, making a total of 94. These individuals had such conditions as lymphadenitis, acute miliary tuberculosis, tuberculous meningitis, pleurisy of the exudative type, peritonitis, tuberculosis of the bones, urogenital tract and the lungs. Among the 94 patients were 53 with primary, secondary or tertiary pulmonary tuberculosis, corresponding to a little more than 3 per cent of the typed specimens from a large group of patients with pulmonary tuberculosis. Secondary and tertiary pulmonary tuberculosis was found in 28 cases. In 9 the disease was rather extensive and in 6, very extensive. The lesions were markedly exudative in 19 of the patients and in 20, cavities were present. Sixteen of these 28 patients had already died when he made his report. Hedvall demonstrated that tuberculosis of bovine origin in man shows complete agreement with the corresponding forms due to the human type of bacilli. The only possibility of establishing the diagnosis is by typing the tubercle bacilli. Thus, the former belief that the bovine type of tubercle bacillus has a low virulence for man is untenable. Similar observations have been made by Griffith and others.

Only 14 of the 67 cases reported in detail were persons living in towns, several of whom had acquired their bovine infection during earlier sojourns in the country. The remaining 53 cases occurred among the rural population. Hedvall states that persons living in the Province of Skåne, whose occupations bring them into a more regular and direct contact with cattle, run a great risk of being infected. In fact, 43 of his 67 cases belong to this category.

Hedvall has demonstrated that the bovine type of tubercle bacillus can be transmitted from cattle to man, from man to man, and from man back to cattle. Therefore he says it is imperative that the campaign against tuberculosis in cattle be carried on with the greatest energy and that the goal must be the extermination of tuberculosis among these animals. He calls attention to the fine work of this nature that is already in progress in Sweden. Obviously the marked reduction of certain forms of tuberculosis in man in the United States is in no small way due to the veterinarians' control of the disease in cattle. This has been so effective that at present only approximately 0.2 per cent of the cattle in this country are infected with tubercle bacilli.

REFERENCES

RAVENEL, M. P.: The intercommunicability of human and bovine tuberculosis, Proc. Path. Soc. Philadelphia, 1902, *23*, 181.

GRIFFITH, A. STANLEY: Observations on the bovine tubercle bacillus in human tuberculosis, Brit. M. J., 1932, p. 501.

GRIFFITH, A. STANLEY: Bovine tuberculosis in man, Tubercle, 1937, *18*, 529.

TOBIESEN, F., JENSEN, K. A., AND LASSEN, H. C. A.: Bovine pulmonary tuberculosis in man. Twenty-six cases from Copenhagen, Tubercle, 1935, *16*, 385.

JENSEN, K. A., AND KIAER, I.: Studies on the types of tubercle bacilli isolated from man, Acta tuberc. Scandinav., 1938, *12*, 105.

LANGE, B.: The role played by bovine tubercle bacilli in human tuberculosis, Brit. M. J., 1932, p. 503.

AMADEO JOAQUIN REY, JULIO CÉSAR PANGAS AND RAÚL JORGE MASSÉ: *Tratado de Tisiologia. Preface by Antonio Cetrangolo. Pp. xxi + 669, with 183 figures, Editor: "El Ateneo," Buenos Aires, 1945, paper.*

By ANTONIO MOLINA

In this book the authors present to us, in concise form, a complete summary of all the fundamental concepts and information relative to the vast field of tuberculosis, which are known as of the present day.

The findings relative to the study of tuberculosis in recent years are so numerous that the general practitioner hardly has time to keep abreast of all that which is published in reviews and monographs. In this respect, the work of Doctors Rey, Pangas and Massé is of great value to students and nonspecialized physicians.

In this third edition which is appearing two years after the previous publication, several topics have been expanded, namely, bronchial tuberculosis, nodular tuberculosis and diferential diagnosis of pulmonary tuberculosis and collapse

therapy. The authors state in the preface that they have deliberately omitted all that which, hypothetically, could be found in the countless chapters written on the study of tuberculosis, and that they are mentioning names or analyzing criteria only when these are new and original or when they are debatable points. They further state that, insofar as possible, they have attempted to adapt and adjust the various tuberculosis trends to the orientation of the Argentinian schools, and avoid all exclusive tendencies.

The book is divided into 58 chapters, an appendix which deals with the tuberculosis of domestic animals and an alphabetical index. Although a large portion of the chapters is dedicated to the tuberculous processes of the respiratory tract, all the various extrapulmonary localizations are adequately treated. Those chapters which are judged to be of secondary interest are set in a smaller type. The hematogenous forms, which contributed so greatly in modifying the classical concepts of the pathology of tuberculosis, are described thoroughly and accurately. In the chapter dealing with the classifications of pulmonary tuberculosis, the authors review the principal categories, giving preference to Bard's classification which enjoys a large following in Argentina. The various chapters concerning pulmonary collapse therapy are also well presented.

In short, it can be stated that this treatise gathers in its pages the most important present day data relative to specialization in tuberculosis, and the various concepts of the Argentinian and American schools of thought. The entire work is written in lucid style and the great number of reproductions of radiographs increases the value of the book which is skilfully published by "El Ateneo."

RUDOLF COBET: *Tuberkulose und Kreislauf. Pp. 96, with 45 illustrations, Berlin and Vienna, Urban & Schwarzenberg, 1941.*

By GEORGE C. LEINER

A comprehensive description of the relation between tuberculosis and circulation is given—according to the author, the first time in the German literature. The correct judgment of the circulatory condition of the patient with pulmonary tuberculosis is of great importance for estimation of the working capacity as well as for the indication of collapse therapy. The first chapter deals with the tuberculosis of the pericardium, myocardium and endocardium. Then, the effects of tuberculosis, especially pulmonary tuberculosis, on the circulation are discussed. The chapters are: Toxic effects on the circulation; disturbance of circulation by mechanical factors; disturbance of pulmonary functions and their effect of collapse therapy on the circulation; respiratory and circulatory function tests in patients with pulmonary tuberculosis; treatment of circulatory disturbances in pulmonary tuberculosis. The last part of the monograph is devoted to the influences of cardiac anomalies on development and course of pulmonary tuberculosis. After each chapter there is an extensive list of references which include the American literature.

Clark W. Heath: *What People Are. A Study of Normal Young Men. In collaboration with Lucien Brouha, Lewise W. Gregory, Carl C. Seltzer, Frederic L. Wells and William L. Woods. Pp. xvi + 141, with 8 figures and 7 tables, Cambridge, Massachusetts, Harvard University Press, 1945, cloth, $2.00.*

By MAX PINNER

"This book is to be regarded as a brief introduction to the point of view of the Grant Study and the methods used in its efforts to study normal human beings." The implications of new and integrated knowledge of the physical, mental and emotional make-up of "normal" men in our modern society of industrialism and competition are practically limitless. Justification of such a study is quite superfluous. The methods and semantics of this type of work will have to be judged on the basis of much more complete records which will be forthcoming, and they may easily become points of controversy.

For the present brief progress report, a few points of interest, which may possibly become the centres of future debates, should be mentioned, without entering into any discussion in the absence of much more complete data and correlations.

The workers in this study have selected "normal" Harvard students. The Study is so fundamental and so definitely a departure from previous mass studies of "normals" that the investigators must be granted the privilege of choosing their own basic terminology. Within this framework, "normal" denotes more than absence of abnormality; it denotes "*balanced*, harmonious blending of functions that produce good integration." (The skeptic may venture to say that "normal," then, is a characteristic of a minority, privileged by nature and experience.)

Next, it may be mentioned that the "normals," selected with considerable care and on the basis of elaborate standards, included, as further studies showed, young men who, according to accepted though vague standards, are not normal, such as men who, under basal conditions, had a pulse rate of up to 105, a range of basal metabolism of −27 to + 26, a systolic blood pressure, on standing, up to 172 and a diastolic up to 106. Similar extremes were found in mental and psychological data. This is not mentioned for the sake of semantic acrobatics around the term "normal," but rather to point out that, in this group of "normals" with an unusually high standard of selection, the range of many physiological functions studied is astoundingly broad.

In the psychological data, the workers chose, probably wisely, not to adhere to any traditional standard terminology, but to choose essentially non-prejudicial descriptive terms. However, many may question whether it was really necessary and sound to start quite as much from scratch in this regard.

There is a stated awareness that the pragmatic usefulness of the standards and judgments employed in this study can be determined only by follow-up observations of periods measured in decades.

Throughout the Study, as presented in this brief introduction, the ultimate

criterion of "normal" is the ability to function properly, to "perform their tasks well;" *one suspects in terms of ultimate success of the individuals studied.* There is no good reason why this should not be a suitable measuring rod. But the skeptic might want to know in what terms success is going to be measured. He might also prefer to see much more definite statements, than the ones that are made, that the frame of reference is our society such as it is to-day. It is just possible that the young man who, in this society, possesses the "*balanced*, harmonious blending of functions" may find himself at sea without compass and without "good integration" if he should be thrown into unexpected situations, or if some essential features of our present society should undergo some basic change in his lifetime. History is full of such individuals who were unable to make the necessary adjustments, even to such common changes as chronic illness or economic depression. Granted that the majority of the subjects studied gave an excellent account of themselves in war service. But the cement of close community life in the Armed Forces may well hold together a personality that may break into chaotic pieces when confronted with problems that he has to face alone. More young men disintegrated mentally and physically *after* the first world war than *during* the war—not counting the victims of direct enemy action. But these are not critical remarks; rather thoughts stimulated by the monograph.

The author points out with profound justification that studies, such as this, are urgently needed to provide rational answers to the question: "education for what?" This book makes it clear that only a study of many physical and psychological aspects of "normals" will pull the answers out of the grip of dogmatic convictions.

The main criticism that occurs to this reviewer is the fact that no correlations are presented between physiological and psychological findings. It might be interesting to know whether marked deviations from customarily accepted averages are likely to occur in regard to physiological *and* psychological functions in the same persons. But such analyses are obviously beyond the scope of the present "introduction." It is hoped that a more definitive report will fill this gap. Such information, be it in the form of positive or negative correlations, may well turn out to be one of the most significant results.

Most readers will undoubtedly find much of profound interest in this "introduction," both as regards methods of investigation and preliminary results.

Harold M. Cavins: *National Health Agencies. A Survey with Especial Reference to Voluntary Associations. Including a Detailed Directory of Major Health Organizations. Pp. 251, Public Affairs Press, Washington, D. C., 1945, cloth, $3.00.*

By E. H. L. CORWIN

Within a brief compass the origin and development of four national professional bodies, *the American Psychiatric Association, the American Medical Association,*

the American Dental Association and the American Public Health Association, and of ten national voluntary health agencies interested in the promotion of their respective public interests are described in this book.

Voluntary promotional health organizations are a characteristically American product. No other country has developed to the same extent counterparts of our voluntary health agencies, and the reason for it is not the American tendency to form societies at the slightest provocation, but rather the dependence of public health promotion in the United States on private initiative. This then answers the fundamental question, What are the characteristics of American thought and life that have made the voluntary health agency posisble?

But, "Why was there no National Tuberculosis Association before 1904? Why did most of the other important voluntary health agencies develop in the fifteen or twenty years after 1904?" The reasons, in so far as the author advances them, are discussed in the summary chapters of the book as well as in connection with the description of the development of each particular national health body. Not all of these descriptions are of equal comprehensiveness for the basic data have not been in equal measure available for each organization. The author has made no effort to consult sources; he uses only what is ready at hand and so, thanks to the work of the late S. Adolphus Knopf, he has apparently had the least difficulty with the National Tuberculosis Association. In the course of this chapter the author brings out the importance which attaches to broad educational efforts in the field of public health. That and the fact that the promotional health associations are composed of laymen of various kinds distinguish them from the professional organizations. The National Tuberculosis Association, the first to focus a nation-wide interest on a single disease, has become the paradigm for other health bodies.

While such professional organizations as the American Medical Association, the National Organization for Public Health Nursing, the American Public Health Association and the American Dental Association draw their support almost entirely from within their respective professional groups, the promotional type of health agency derives its financial support from gifts, endowments and individual and corporate contributions. Thus, although the direction of the health agencies comes from professional groups, the membership and support come almost wholly from the laity. The other difference lies in the fact that while the professions must needs concern themselves chiefly with matters of ethics, professional education and standards, and the furthering of professional interests, the promotional organizations devote themselves to socio-medical problems, to the expediting of social justice and to the stimulation of scientific or quasi-scientific research. "With or without bias, their chief weapon has been the promotion of ideas or of knowledge, through education, publicity, and propaganda. They have promoted, instigated, or initiated investigations, demonstrations, experiments, research, and legislation. They have courted and used the professions; in some instances they have tried to educate them. But the lay public is their field of activity, their source of support, and their final judge. With the public's acceptance of their program, they rise or fall."

Though the author has not undertaken a critical evaluation of the agencies that he has discussed, his skilful factual handling of the available data makes this book not a directory but a valuable sociological study.

René J. Dubos: *The Bacterial Cell. In Its Relation to Problems of Virulence, Immunity and Chemotherapy. With an Addendum by C. F. Robinow. Pp. xix + 460, Cambridge, Massachusetts, Harvard University Press, 1945, cloth, $5.00.*

By MAX B. LURIE

This book is a singular and timely contribution from an expert toward a clarification and integration of recently acquired bacteriological knowledge from the standpoint of biological science and largely from the point of view of biochemistry. It does not intend to present exhaustive data on all the problems involved but rather, by the citation of striking data widely scattered in the literature, to give substance to the essential biochemical, pharmacological and physiological properties of bacteria which control their cytology, influence their growth, variability and plasticity, determine the intricate host-parasite relationships which result in virulence and communicability, fashion the essential stoechiometric chemical phenomena which constitute antigen-antibody reactions and enzyme activity, explain the staining properties of bacteria and their phylogenetic classification, throw light on the mode of action of antiseptics and give both esoteric and practical information on the mode of action of chemotherapeutic agents.

The book is divided into 8 chapters. The first deals with the complexity of the bacterial cell and stresses the interpretation that the apparent unity of bacteria is largely determined by their size and by the methods available for their study, rather than by their intrinsic biological similarity. It also gives a tentative phylogeny of bacteria in which tubercle bacilli are classed with streptococci and other gram-positive bacteria. In the next chapter, on bacterial cytology, the author shows how, by means of ultraviolet radiation and specific color tests, chemical definition of morphological entities can be given. He reviews the recent data obtained by the electron microscope on the more intimate structure of the bacteria, the rigid cell wall, the cytoplasmic membrane and the inner cytoplasm. He describes the tubular structure of the flagella and their mode of function as motile organs. The capsular material, both the carbohydrate of the pneumococcus and the M protein substance of streptococci, is noted and their importance in virulence is stressed. He then takes up the physiochemical behavior of bacteria and demonstrates that the mechanism of staining involves an ionic exchange. Acid dyes are absorbed on bacteria in acid reaction, whereas basic dyes act better in an alkaline reaction. Gram-negative bacteria have an isoelectric point of pH 5 to 6 and hence have an affinity for acid dyes, whereas gram-positive bacteria have a more acid isoelectric point, around pH 2, and therefore have a greater affinity for basic dyes. The acid-fastness of tubercle bacilli is probably due to mycolic acid which is present in a combined form and imparts to the cell its tinctorial characters. Hence mechanical disintegration of tubercle

bacilli robs them of their acid-fastness, just as autolytic enzymes destroy the gram-positive properties of certain bacteria. He discusses the flagellar and somatic antigens of gram-negative bacteria and points out their importance in virulence, in colonial form of R or S and the rather novel idea of the stratification of the antigen on the bacterial cell. Those antigens situated on the surface of the bacterial cell are most important in resistance. Antibodies are globulins, and high molecular substances cannot penetrate the surface membrane. He discusses the rôle of enzymes obtained from nonspecific sources which can hydrolize some of the surface substances, such as the capsule of the pneumococcus and become efficient chemotherapeutic agents against the disease. An enlightening chapter on bacterial variability follows. He points out how, because of the great rapidity of multiplication of bacteria, their innate property of variability without concomitant lethal tendencies results in adaptive changes which are temporary and determined by environmental conditions on the one hand, or stable and inherited on the other. Natural selection quickly eliminates the variants which are unsuited to a given milieu. Drug fastness is merely due to the survival of the few cells which are innately resistant to the deleterious drug, to which the majority succumb. Increase of virulence by animal passage is accomplished by the same laws of natural selection. One of the most fascinating and biologically most important observations is the transformation of rough, nonencapsulated, avirulent pneumococci into an encapsulated highly virulent organism of a given type and the isolation in pure form of the transforming substance. The chapter on virulence is highly instructive. Virulence is not merely a property of the infecting agent but results from the whole gamut of interactions of the parasite and host which determine the pathogenic career of the bacterium. A point which is rarely countenanced is that an organism may be highly virulent on inoculation into animals and yet have little if any capacity to spread in a community, that is, it has little communicability. Yet the converse may be true. Also enlightening is the discussion on immunization. While it is true that the antigens situated on the surface of the bacterial cell are important, they are not the only ones effective in the process. Rough pneumococci can act as effective immunizing agents. It is the chemical composition of the antigen which is important in this function.

The chapter on bacteriostatic and bactericidal agents should be most carefully studied, especially by all those who are engaged in chemotherapeutic research. Doctor Dubos shows that antiseptics, like Hg and As, do not act as general protoplasmic poisons by their capacity to precipitate proteins, but rather by their affinity for the Sh radicals of bacteria. He cites how organisms that have been "killed" by these metals can be "revived" by the addition of an excess H_2S. Similarly, bacteria that have been inhibited by acid or basic dyes can be made to grow out again by a mere change in the reaction of the system. The bacteriostatic action of sulfonamides and similar substances is due to the combination between them and an essential enzyme which acts on a substrate similar to paramino-benzoic acid with which the sulfonamides share certain prosthetic radicals. Hence an excess of paramino-benzoic acid will inhibit the bacteriostatic action of the drug.

Enough, it would seem to me, has been said to form an idea of the essential nature of the book. It is clearly written, thoroughly integrated and highly enlightening. There are a few typographical errors, but outside of this one cannot take exception to the excellence of the contribution. There is an extended bibliography and an excellent index which still further enhance the value of the book.

EINAR HOLLSTROM: *An Investigation into a Yeast-like Fungus Isolated from Patients Suffering from, or Suspected of, Pulmonary Tuberculosis. Acta Medica Scandinavica, Supplementum CXLIV, Uppsala 1948, Almqvist & Wiksells Boktryckeri A.-B., pp. 107, and 22 plates with explanations.*

By DAVID T. SMITH

This investigation was carried out at the Institute of Hygiene and Bacteriology at the University of Upsala. A part of the cost of the study was contributed by the Swedish Anti-Tuberculosis League.

The apparent purpose of this study was to reinvestigate the claim of Reenstierna in 1912 that yeast cells gave rise to Koch's bacillus when grown on glycerine bouillon. He refers also to the studies of Gullberg, 1933–1935, who isolated a yeast-like organism from the sputum of 2 patients with pulmonary tuberculosis. Subcultures in glycerine bouillon from single cell cultures of the yeast gave rise to acid-fast rods of Koch's type.

The author isolated strains of a yeast-like organism from patients with tuberculosis, or suspected of having tuberculosis. In 2 instances the yeasts were isolated from sputum and in the other 3 from gastric washings. The organisms fermented glucose, maltose and levulose, but not galactose and saccharose. They were identified by the author as *Monilia pinoyi* (Castellani), which has now been reduced in synonomy to *Candida albicans*. After twelve months, on artificial media, pure line strains were established by the isolation of a single yeast cell for subculture. We can accept the author's evidence that these cultures contained no acid-fast organism. These yeast cultures had a somewhat reduced virulence for rabbits. Large doses killed the animals in ten to fifteen days, while smaller doses caused loss of weight and, in some instances, after months, focal lesions in the eyes and brain from which the original yeasts were recovered by culture.

In 5 glycerine bouillon cultures from 3 of the yeast strains originating from single cells, there appeared among the fungus cells acid-fast rods. Five guinea pigs were inoculated with material from 3 of the bouillon cultures containing acid-fast rods. Some of the animals developed small, localized abscesses in the groin, but disease of the internal organs was not produced in any of the 5 guinea pigs.

More than 40 rabbits were inoculated intravenously with yeast cultures grown on glycerine bouillon. Acid-fast organisms were not demonstrated in these cultures before inoculation. It is not clear whether they were sought for and not found, or whether they were inoculated without an examination of the inoculum

for acid-fast rods. Acid-fast rods were found on smears from one or more organs in 4 of these rabbits. Both yeast cells and acid-fast organisms were grown from the organs of R.589. Acid-fast organism alone from R.527.

The mixed culture of yeast and acid-fast rods from R.589 was inoculated into guinea pigs and rabbits. Progressive disease did not develop and acid-fast organisms could not be isolated.

The diseased organs of R.527 were inoculated into 2 rabbits and 3 guinea pigs. The guinea pigs were not infected, but one of the rabbits developed a disease resembling tuberculosis. Subinoculations were made in 2 rabbits and 3 guinea pigs. Again, the guinea pigs failed to develop disease, but extensive disease of spleen and liver appeared in both rabbits. Typical acid-fast organisms were isolated from the organs of both rabbits. These cultures of acid-fast organisms were highly pathogenic for rabbits but only slightly pathogenic for guinea pigs. The author gives no conclusion as to the type of tubercle bacillus recovered, but his inoculation experiments suggest that his rabbit R.527 was infected with an avian bacillus.

In the entire study, acid-fast rods resembling tubercle bacilli were observed in 5 glycerine broth cultures made directly from the single cell yeast cultures in the organs of 5 rabbits inoculated with cultures of yeast grown in glycerine broth. With the single exception of R.527 all attempts to isolate the acid-fast rods from cultures of animal tissue resulted in failure.

The evidence presented in regard to R.527 is very convincing. The infection appeared three to six months after the intravenous injection of a glycerine broth culture of yeast cells. The gross and microscopic appearance of the lesions were consistent with tuberculosis. Pure cultures of acid-fast organisms resembling tubercle bacilli were obtained. The disease was passed through two consecutive series of rabbits by the inoculation of infected tissue. Pure cultures of tubercle bacilli were isolated from both the first and second passage, and cultures were highly pathogenic for rabbits, but only slightly pathogenic for guinea pigs.

The question whether the tubercle bacillus isolated from R.527 arose by a series of mutations from a single cell culture of a yeast-like organism, or was an accidental infection in the laboratory cannot be settled without more work.

This monograph contains 107 pages, not counting the illustrations, and a bibliography of 134 references, with 22 plates and 95 figures, of which 45 are in color.

Brief Comment

R. Y. Keers and B. G. Rigden: *Pulmonary Tuberculosis. A Handbook for Students and Practitioners. With a Foreword by F. H. Young. Pp. xii + 278, with 124 figures, The Williams & Wilkins Company, Baltimore, 1945, cloth, $5.00.*

It was the authors' aim to write "as briefly and as clearly as possible" a textbook "primarily for the student and practitioner." While they have admirably achieved their purpose in the practical clinical portions of the book, in the brief

chapters on Bacteriology, Pathology, and Epidemiology and Resistance, it appears that accuracy has, at times, been sacrificed for brevity and simplicity. However, it is more important to emphasize that the clinical chapters are lucid and, according to the plan of the book, free of unessential detail. Even the busiest practitioner should find time to read the small 250 pages, especially since they are interspersed with intelligently chosen and excellently reproduced full-page roentgenograms. If all practitioners could be persuaded to read and digest this text, few cases of pulmonary tuberculosis would leave their offices without a correct diagnosis.

The relatively long chapter on Collapse Therapy is sound and well balanced and is illustrated by 43 roentgenograms, in the selection of which the authors have shown excellent judgment. While it may be difficult to find several groups of phthisiotherapists to agree fully on collapse treatment, there are probably few who would frankly disagree with the authors' statements on this subject.

The very brevity of this book is witness to the authors' mastery of their subject. It is warmly recommended for the groups of readers for which it is intended—with the hope, as the authors put it, that they may "be encouraged to pursue the matter further."

Tuberculosis in the United States. Graphic Presentation. Volume 3. Mortality Statistics for Cities of 100,000 or more Population by Age, Sex and Race, 1939–41. Prepared by the staff of the Field Studies Section of the Tuberculosis Control Division, U. S. Public Health Service, under the direction of Carroll E. Palmer, M.D. Medical Research Committee, National Tuberculosis Association, 1945, paper.

The major portions of the Foreword of this publication are quoted:

"The volumes of this series, *Tuberculosis in the United States, Graphic Presentation*, are the result of a cooperative undertaking by the National Tuberculosis Association and the U. S. Public Health Service. The basic data were made available by the U. S. Bureau of the Census.

"For each State, and for the several sex and race groups, the first volume in this series presented tuberculosis mortality rates by age, while the second volume presented proportionate mortality by age. These data are basic to a determination of the magnitude of the tuberculosis problem in the States. States, however, are areas which do not ordinarily encompass homogeneous populations and great variety is found within their borders with respect to many factors. Place of residence is an important factor in tuberculosis mortality. During the three-year period, 1939–41, rural residents sustained an average annual death rate from tuberculosis of 41.0 per 100,000 population, while the mortality rate in the large American cities of 100,000 or more population was 55.4, over one-third higher. The relatively high tuberculosis mortality rates of the large cities may often be submerged in the over-all rates of the States in which they are located and it is, therefore, advisable for workers in the field of tuberculosis control to have at hand, in as much detail as possible, mortality data for population groupings of various sizes. This volume is an attempt to meet a part of the need by present-

ing the tuberculosis mortality record for the period 1939–41 for the 92 cities of 100,000 or more population at the time of the 1940 Census enumeration."

"The present volume presents two tables and two charts for each of the 92 cities. The first table presented for each city contains, for the period 1939–41, basic data on population, deaths from tuberculosis, and death rates for tuberculosis (all forms), by age, sex and race. The second table for each city contains, for the period 1939–41, the number of deaths from all causes and the percentage of those deaths that were due to tuberculosis (all forms) by age, sex and race. Specifically, the charts in this volume present for each city:

6. Tuberculosis mortality, average annual rate by age, sex and race, 1939–41.
7. Deaths from tuberculosis as percentages of deaths from all causes by age, sex and race, 1939–41.

"The tables and charts are numbered to follow serially those shown in Volume 2. The number for each table or chart is followed by a pair of digits identifying the State in which the city is located (the first digit selecting the geographic division). This is followed by a single digit designating the alphabetical rank of the city within the State.

"In order to facilitate comparisons between cities, the crude rates and ratios for all races were standardized for age and race and the specific sex-race rates and ratios were standardized for age. To accomplish this, age-specific rates of a given sex-race group for the different cities were applied to a corresponding standard population of four broad age groups. The standard population employed in adjusting the tuberculosis death rates for each of the sex-race groups was the total population of that group residing in the 92 cities in 1940. Standardization for proportionate mortality was accomplished in a similar manner, using the distribution by age of the deaths from all causes for each sex-race group for 1940.

"Three bar diagrams ranking the cities according to crude tuberculosis death rates for all races, whites and nonwhites are introduced at the beginning of this volume. These are followed by three bar diagrams which rank the cities according to proportionate mortality (not standardized), and are likewise shown for all races, whites and nonwhites. For the 53 cities with no race breakdown, the rates and ratios for all races have been used in the diagrams for whites. These may be assumed to approximate closely the rates and ratios of the white populations since the proportion of nonwhites in these cities was relatively small."

Books Received

L. R. Broster: Endocrine Man. A Study in the Surgery of Sex. With a Foreword by Sir Peter Chalmers Mitchell. Pp. xi + 144, New York, Grune and Stratton, 1945, cloth, $3.50.

Hugo Dooner: La silicosis pulmonar. Pp. 195, with 23 figures, Empresa Editora Zig-Zag, S. A., Santiago de Chile, 1944, fabrikoid.

SELSKAR M. GUNN AND PHILIP S. PLATT: Voluntary Health Agencies. An Interpretive Study. With a Foreword by Louis I. Dublin. Under the auspices of the National Health Council. Pp. xvii + 364, The Ronald Press Company, New York, 1945, cloth, $3.00.

RUDOLF HÖBER: Physical Chemistry of Cells and Tissues. With the collaboration of David I. Hitchcock, J. B. Bateman, David R. Goddard and Wallace O. Fenn. Pp. xiii + 676, with 70 illustrations, The Blakiston Company, Philadelphia—Toronto, 1945, fabrikoid, $9.00.

JOSEPH W. MOUNTIN, ELLIOTT H. PENNELL AND VANE M. HOGE: Health Service Areas. Requirements for General Hospitals and Health Centers. Public Health Bulletin No. 292. From the Division of States Relations, Bureau of State Services. Prepared by Direction of the Surgeon General. United States Government Printing Office, Washington, 1945. For sale by the Superintendent of Documents, Washington, D. C., 25 cents.

MANUEL TAPIA: Formas Anatomoclínicas, Diagnóstico y Tratamiento de la Tuberculosis Pulmonar. Pp. 503, with 492 illustrations, Livraria Luso-Espanhola, Lda., Rua Nova do Almada, Lisboa, 1945, paper.

Publicaciones del Centro de Investigaciones Tisiologicas. Volumen VIII. Director: Prof. Roque A. Izzo. Pp. 420, Pabellon "Las Provincias," Hospital Tornu, Buenos Aires, 1944, paper.

Rhode Island State Sanatorium. Forty Eventful Years, 1905–1945. Pp. 84.

Tercera Reunion Clinica Anual—1945. Tema: Experiencia sobre tuberculosis. Prof. H. Orrego P., Secretario general. Dr. Santiago Raddatz, Prosecretario. Servicios de Beneficencia y Asistencia Social, Hospital del Salvador, Director: Dr. Rogelio Erazo. Santiago de Chile. Pp. 189, paper.

AMERICAN TRUDEAU SOCIETY

Report of the Membership Committee

Dr. Harold G. Trimble, *Chairman*
Dr. David A. Cooper Dr. Carl Mulky

This is the report of your Membership Committee since the last annual meeting in 1944. The Membership Committee has been directed upon numerous occasions by the Executive Committee and the Council that its function was twofold: First, to pass upon the names of doctors applying for membership. Second, to actively promote membership in our Society. The active details of this work are carried on by Dr. Cameron St. C. Guild and Mr. L. E. Lascelle in our New York office, and your Membership Committee acts essentially in an advisory capacity.

The names of applicants for membership are submitted on our approved forms. The essential data are sent to a member of our Council or Advisory Board in the respective area. If the Council or Advisory Board member does not know the applicant, we request him to ascertain through local sources available to him if the applicant will make a desirable member, keeping in mind that we are not an organization of specialists alone, but that membership is open to all reputable physicians who have an interest in our work. This method seems to function adequately and to fill our rather simple needs. With regard to activities in increasing the membership, you will note that the most productive method has been the interest of our present members. We have attempted to stimulate this by simple reminders from time to time.

The Eastern Section of the Trudeau Society has a requirement that their associate members must become active members in the American Trudeau Society within a certain period of time. Through Dr. James C. Walsh, the Secretary of the Eastern Section, their associate members were informed of this requirement, and provided with application blanks for the American Trudeau Society. When our President, Julius Wilson, attended the first Mexican Congress of Tuberculosis in Mexico, he had an opportunity to stimulate membership from that area. Dr. Guild, while on an official visit to Canada in the fall of 1944, had membership in mind, and his work was productive of good results. Many other members have made substantial contributions to our work.

There is usually a marked stimulation of membership applications at the time of the Annual Meeting. As there will be no meeting this year (1945), this stimulus, of course, will be lacking. Your Membership Committee has therefore renewed its efforts in asking the coöperation of the officers, Council and Advisory Board members to canvass the list of our present members in their respective areas and advise us of the names of such additional men who would likely be interested in our work. We found that the most effective way is to have these members of the Council and Advisory Board write personal letters themselves.

The actual physical labor of this can be done in our New York office. If this does not seem feasible, we ask permission to use their names in writing to these prospective members.

The following is the status of our membership as of May 1, 1945:

Active members	2,143
Provisional members	194
Total	2,337

AMERICAN TRUDEAU SOCIETY

Report of the Committee on Undergraduate Medical Education

Dr. Frank L. Jennings, *Chairman*

Dr. Robert G. Bloch	Dr. C. Howard Marcy
Dr. Harold M. Coon	Dr. Sidney J. Shipman
Dr. Reuben J. Erickson	Dr. John H. Skavlem

During the past year various members of the Committee on Undergraduate Medical Education visited the following Universities: Syracuse, Western Reserve, Jefferson, Pennsylvania and Temple. In addition, the Universities of Oregon, California, Southern California and College of Medical Evangelists were contacted by Dr. Shipman.

In all the schools it was found that there was a reduction in the teaching staff occasioned by the war. An effort had been made by the remaining staff members to carry out both clinical and didactic work.

There had also been an evident reduction in the health survey of the students. This seemed to be the result of two conditions: first, the reduced staff, and second, the fact that the armed forces have taken such complete charge of the students. In only two medical colleges did the Committee find any particular measures such as masks and gowns used in the prevention of tuberculosis among the students.

The annual survey for tuberculosis by X-ray and tuberculin, as well as special precautionary methods against tuberculosis, appear to be projects to which future committees should devote considerable time and effort.

All members of the Committee, excepting Dr. Shipman, met in Philadelphia in December. The Committee has been anxious for some time to stimulate interest in tuberculosis among medical students. As a result it had invited several authors to submit outlines of their ideas for a pamphlet which would bring about this result. Two such outlines were reviewed in Philadelphia but only one was looked upon with favor. This outline presented various aspects of tuberculosis by characterization and fact. The Committee asked to have this material reproduced so that each individual member and other interested people might review it more critically. As yet no definite decision has been made on the matter.

The Committee did consider favorably the sending of reprints from the AMERICAN REVIEW OF TUBERCULOSIS to each senior medical student in all of the Universities. The consensus was that two or three articles annually could be selected which would stimulate the students' interest in chest diseases.

AMERICAN TRUDEAU SOCIETY

Report of the Sub-Committee on Sanatorium Planning and Construction

Dr. Hugh B. Campbell, *Chairman*
Dr. Robert E. Plunkett — *Mr. J. B. Basil
Dr. R. D. Thompson — *Miss Suzanne H. Harrison

It will be recalled that at the last meeting of the Executive Committee of the American Trudeau Society, this Committee reported its inability to secure essential information on its various problems, chiefly because the first questionnaire sent to sanatorium superintendents and administrators throughout the United States was too long. The busy executives did not have the necessary time to supply the information wanted.

A meeting of the Committee was held at the Hotel Pennsylvania on November 20, 1944. In addition to the members, there were also present Dr. Kendall Emerson and Mrs. Elizabeth Stoltenkamp of the National Tuberculosis Association, Dr. Cameron St. C. Guild, Executive Secretary of the American Trudeau Society and, by invitation, Dr. C. M. Sharp, substituting for Dr. Herman Hilleboe of the United States Public Health Service and Mr. Marshall Shafer, Chief Architect of the Hospital Facilities Section of the United States Public Health Service. Since the United States Public Health Service has a construction problem, it was felt that a meeting of the representatives of the two organizations would be mutually helpful.

It was immediately decided at this meeting that a short questionnaire, not to exceed two pages, would be sent to a group of sanatorium administrators throughout the country. It was also agreed that it would be advantageous for Mr. Basil to visit a group of sanatoria, not to exceed five or six, that first-hand information might be obtained from unrelated sources. A motion was voted requesting the National Tuberculosis Association to set aside a sufficient sum of money to take care of Mr. Basil's expense for this investigation.

It should be evident that the Committee has been and is endeavoring to collect information which can be properly correlated, not to the satisfaction of all, but that those seeking information or advice on sanatorium construction can have a guide which will contain essential hospital needs and space allotment for the same. It is further to be recognized that construction needs must be adapted to urban and rural locations as well as geographical distributions.

The two-page questionnaire was distributed. Mr. Basil made his visits and a meeting of the Committee was held again at the Hotel Pennsylvania in New York on April 30, 1945. At that time, there were present, in addition to the members of the Committee, Dr. Kendall Emerson, Managing Director of the National Tuberculosis Association; Mrs. Elizabeth Stoltenkamp, Administrative Assistant to Dr. Emerson; Dr. Cameron St. C. Guild, Executive Secretary of the American Trudeau Society; Dr. Ralph Horton, Chairman, and Dr. Victor F.

* National Tuberculosis Association Members.

Cullen, member, Committee on Sanatorium Standards; Dr. H. McLeod Riggins, Chairman of the Medical Advisory Committee on Health Education; and Mr. Marshall Shafer, Chief Architect of the Hospital Facilities Section of the United States Public Health Service.

Again it was immediately apparent that there were widely divergent views on practically every problem which has to do with sanatorium construction and maintenance. These differences exist as to whether a sanatorium should be one or two stories or multi-storied; with porches or without porches; with light treatment in groups or individual rooms; food service in dining room or to the patient in the bed in all cases; width of corridors; proper allocation for out-patient department; number of pneumothorax rooms essential; single, two-bed or four-bed rooms; distriubtion of beds for males and females; space necessary for accommodation of personnel. These and many other problems have been under discussion time and again. All problems will not have been solved to the satisfaction of all, but we believe we will be able to present a guide which will be helpful to those faced with the problem of sanatorium construction. It seems likely that this final plan will be available in the near future.

NOTICE

United States Public Health Service

January 17, 1946

Appointments to fill vacancies in the Reserve Corps of the United States Public Health Service are now being made, and examinations for Regular Corps appointments will be held in April and May, Surgeon General Thomas Parran announced to-day.

Physicians, dentists, and nurses are needed immediately for duty in hospitals, in the Tuberculosis and Venereal Disease Control programs, and in other activities of the Public Health Service.

Pay and allowances, established by law, are identical with those for medical officers of the Army. All travel expenses, including travel to first station, are paid by the Service.

In announcing the recruitment campaign, Dr. Parran stated: "For the physician, the dentist, and the nurse, the Public Health Service is unique in the variety of opportunities it offers. Not only does the person have the opportunity for outstanding service to the nation in the growing field of Public Health, but the opportunities for professional growth and development are almost limitless. There is clinical work in Public Health Service hospitals throughout the country. The importance of medical research is being emphasized to-day more and more and in the Public Health Service research opportunities exist in both laboratory and the field. Institutional, public health, and administrative work is offered nurses. Whether a professional person is embarking on his career, or has already elected the field in which he wishes to specialize, the Public Health Service, I sincerely believe, offers him much that he is seeking."

Appointments to the Reserve Corps are made on a basis of review of data furnished by the applicant. Physical examination is required.

Regular Corps appointments require appearance before a Board, and a written professional examination. Dates and places for the examination will be announced shortly.

The Service pointed out that a person receiving an appointment in the Reserve Corps immediately, may, if he desires, take the examination for the Regular Corps at the time they are held.

Those interested in either immediate appointment in the Reserve Corps, or in taking the examination for the Regular Corps, should request application forms of the Surgeon General, U. S. Public Health Service, Washington, D. C., Federal Security Agency.

NOTICE

The American College of Physicians

The American College of Physicians will resume its Annual Meetings this year. The 1946 meeting will be held in Philadelphia, May 13 to 17, inclusive, with headquarters at the Philadelphia Municipal Auditorium, 34th Street below Spruce.

The meeting will be conducted under the Presidency of Dr. Ernest E. Irons, Chicago, Illinois, and the General Chairmanship of Dr. George Morris Piersol, Philadelphia, Pennsylvania.

STANDARDIZATION OF PHOTOFLUOROGRAPHIC EQUIPMENT

RUSSELL H. MORGAN[1] AND WILLARD W. VAN ALLEN[1]

During the past year, facilities for manufacturing roentgenographic equipment, designed especially for tuberculosis case-finding, have undergone a considerable expansion in the United States. In addition to the General Electric and Westinghouse Corporations who have been producing small-film equipment for some time, the field now includes such companies as Picker, Kelley-Koett, North American Philips, and Mattern. All of these companies plan to devote most of their attention to the manufacture of 70 mm. photofluorographic apparatus, although the General Electric Corporation will continue its line of 4 x 5 inch equipment and the Westinghouse Electric Corporation will make available 35 mm. apparatus.

In general, the large number of manufacturers producing mass roentgenographic equipment represents a desirable situation, for it provides the consumer a better opportunity to obtain the apparatus which will best satisfy his needs. It must be recognized, however, that the situation also presents a number of problems. Early in 1945 when the several X-ray companies submitted to the Tuberculosis Control Division plans of the photofluorographic equipment which they proposed to manufacture, it became apparent that a wide variety of designs was contemplated. Some manufacturers proposed the use of a photofluorographic screen which emits yellow light; such a screen, of course, requires a film especially sensitive in the yellow portion of the spectrum. Other manufacturers planned the use of a screen which emits blue light and requires a film sensitive to blue radiation for optimum results. In addition to differences in the type of screen there was also considerable variation of screen size. One manufacturer planned a screen 16 inches square; several others wished to employ a 15 x 17 inch screen, while another considered a screen 15 x 16 inches optimal. Since the size of the screen determines the size of the image on the photofluorographic film, and thereby the design of the masking devices in the film magazine of the photofluorographic camera, as well as the viewing equipment with which the films are interpreted, this variation in screen size reflected a similar variation in the design of the camera and viewing equipment. Variation was also contemplated in the mechanism for shifting the X-ray tube in equipment providing stereoscopic films. Some manufacturers planned the use of 4 inch tube-shift, whereas others considered a movement of 2.5 inches. The place where the greatest variation was observed was in the design of the X-ray tube and its associated high-voltage cables. Although five of the six X-ray manufacturers obtain their X-ray tubes and high-voltage cables from common sources of supply, each equips its tubes and cables with terminals unlike those of any other. Accordingly, a tube or cable sold by one company cannot be used with the apparatus of another, even

[1] From the Radiology Section, Tuberculosis Control Division, United States Public Health Service, Washington, D.C

though the tubes and cables of the two companies are almost identical in gross appearance and in their electrical characteristics.

This variation in equipment design presents several obvious disadvantages. First, the price of photofluorographic apparatus is made unnecessarily high, since the lack of coördination of effort increases manufacturing cost. Second, it may frequently cause annoying difficulties in the supply and maintenance of an agency's equipment. For example, if a tuberculosis association or health department has two units one of which requires blue-sensitive film and one of which requires film of yellow sensitivity, it is probable that one or both units will occasionally be supplied with the wrong kind of film, unless great care is taken by the supply officer. The same problem will present itself when replacement of defective X-ray tubes and cables is necessary.

The problems associated with variation in the design of photofluorographic viewing equipment, both single and stereoscopic, are also of some importance. It is anticipated that, as mass case-finding programs develop, there will be an increasing exchange of films between the agencies conducting the surveys and the physicians to whom the positive cases are referred. In most instances the viewing equipment of the physician will not be of the same manufacture as the one producing the photofluorograph with which the film is made. Difficulties, therefore, will arise when the physician attempts to interpret the film, because the image size will be either too large or too small to be accommodated in the viewer at his disposal. The difficulties will be particularly severe when the films are stereoscopic, for then the physician not only will experience difficulty in positioning the films properly, but also will experience trouble in fusing the two images.

The foregoing problems might be effectively eliminated, or at least greatly minimized, if the manufacturers who produce photofluorographic equipment adopted certain basic standards of design. In an effort to bring about such standardization the Tuberculosis Control Division of the U. S. Public Health Service requested the National Electric Manufacturers Association, early in June, 1945, to call a meeting of representatives of the X-ray industry for preliminary discussions on the subject. It was recommended that consideration be given the following problems:

1: Standardization of the design of X-ray tubes and high-voltage cables.
2: Standardization of the types of photofluorographic films and screens.
3: Standardization of the size of photofluorographic screens.
4: Standardization of the distance the X-ray tube is moved in stereoscopy.

The meeting was held on July 9, 1945, and attended by a large number of representatives from the X-ray industry. All exhibited a sincere desire to coöperate in the standardization program as set forth by the Tuberculosis Control Division. The several problems were discussed at length and the Radiology Section of the Division was requested to accumulate reliable quantitative data with which the formulation of a set of standards might be facilitated.

In the several weeks following the meeting, the Radiology Section undertook this study. First, the most suitable type of film for photofluorographic use was investigated. After careful testing it was found that the blue-sensitive films which are available to-day possess somewhat greater speed than those of yellow-sensitivity, but that the latter have a slight advantage in their ability to record detail. The film manufacturers, however, are confident that these minor differences may be readily equalized and that technically the two films may be made equally satisfactory. From a practical standpoint, however, the yellow-sensitive film requires more stringent lighting conditions in the darkroom during processing than those necessary when blue-sensitive film is developed. Furthermore, many photofluorographic units will be installed in hospitals having darkrooms already equipped for the processing of blue-sensitive film (ordinary X-ray film is of the blue-sensitive type). Accordingly, the suggestion was made by the Radiology Section that the X-ray manufacturers adopt for photofluorography the use of the blue-sensitive film and its corresponding blue-emitting fluorescent screen.

The second problem studied was that concerning the optimal size of the photofluorographic screen. In this investigation, some three thousand photofluorograms were studied to determine the limits of variation of chest size among the general population. All of the films were made with a photofluorograph having a tube-screen distance of 40 inches. In this group of films none was found in which the image of the chest on the photofluorographic screen exceeded a maximum width of 15 inches from rib margin on the left side to rib margin on the right side. There was one individual whose chest image exceeded 14 inches, 8 persons whose chest image exceeded 13 inches and 27 whose chest image exceeded 12 inches. From these results it seemed reasonable to suggest that the photofluorographic screen be no wider than 15 inches. With careful centering such a screen would include the chests of all persons normally encountered and in the great majority of cases would leave some leeway to the technician in centering. The length of the screen did not appear to be a critical problem and, since most of the manufacturers planned to use a screen 17 inches long, such a length was recommended as a standard.

The image produced by the 15 inch by 17 inch screen occupies a space on 70 mm. film approximately 2.5 inches wide and 3 inches long. Accordingly, so that there might be standardization in regard to the viewing equipment for stereoscopic films, it was suggested that the distance from the centres of successive films be 3.25 inches.

In regard to the distance the X-ray tube should move in stereoscopy, Kurtz (1) has shown that, for correct depth perception, this distance should be equal to the interpupillary distance of the observer divided by the magnification of the overall photofluorographic system (magnification of the photofluorogram, itself, multiplied by the magnification of the stereoscope). If the distance between the X-ray tube and the photofluorographic screen is 40 inches, the distance which most of the manufacturers planned to employ, the eyestrain which an observer experiences when interpreting stereoscopic films will approach a minimum when

the magnification of the overall photofluorographic system is in unity. Therefore, the stereoscopic shift of the X-ray tube should equal the normal interpupillary distance of 2.5 inches.

As a result of the foregoing investigations, the following recommendations were made to the X-ray manufacturers:

1: The photofluorographic film should be of the blue-sensitive type.
2: The photofluorographic screen should be of the blue-emitting type.
3: The photofluorographic screen should be 15 x 17 inches in size.
4: The distance from the X-ray tube to the photofluorographic screen should be 40 inches.
5: The X-ray tube shift for stereoscopy should be 2.5 inches.
6: The distance between the centres of successive exposures on the 70 mm. film-roll should be 3.25 inches.

Of the six companies producing photofluorographic equipment, five have adopted the above recommendations in their entirety. At this writing the Westinghouse Corporation has not defined its policy. It is inclined to favor the use of a screen 16 x 16 inches and points out that with such a screen it is possible to obtain approximately 20 per cent more exposures per roll of film than is possible with a 15 x 17 inch screen. This advantage, however, is largely counteracted by the fact that the area of the chest image as seen on the film is approximately 14 per cent greater when a 15 x 17 inch screen is used than is the case when the screen's size is 16 x 16 inches.

Decisions regarding the standardization of X-ray tubes and cables have been deferred pending further discussion. Contrary to general impression, the problems associated with such standardization are extremely complex, involving for a period of years a duplication of manufacturers' inventories in warehouses throughout the country. Nevertheless, a sincere willingness to establish a unified design has been expressed by company engineers, and it is expected that much progress will be made during the next few years. It is possible that before long higher kilovoltages than those now employed in photofluorography will be used routinely. Such a trend will make mandatory the redesign of present-day tubes and cables. The manufacturers have indicated that, when these new designs are under discussion, there will be a free interchange of information, thereby laying the foundations for standardization. At the present time the Radiology Section is investigating the kilovoltage range at which greatest efficiency and image clarity occur under photofluorographic conditions. As soon as this kilovoltage is determined discussions on new tube and cable designs will be immediately initiated.

The standardization program as outlined in the foregoing paragraphs doubtless will be expanded as time goes on. Some people have urged that it be developed to the point where all photofluorographic equipment, regardless of manufacture, be essentially identical. They point out that under this condition the several X-ray manufacturers could pool their resources to provide greatly improved facilities for the servicing of defective equipment in the field. However, such

extreme standardization is probably not only impractical but undesirable, for it would almost certainly curtail research in photofluorographic design. It will be observed that, in the recommendations made by the Tuberculosis Control Division in regard to standardization, none of the recommendations involved items which by their standardization would stifle investigation and research in the field of mass radiography. Such an attitude will continue to be the policy of the Tuberculosis Control Division and, by it, it is felt that the maximum benefits will be made available to the greatest number of consumers of X-ray equipment.

SUMMARY

During the past year the availability of roentgenographic equipment designed especially for tuberculosis case-finding has increased markedly. Whereas previously there had been but two companies producing photofluorographic equipment in the United States, there are now six.

In an effort to bring about standardization in basic design of the various photofluorographic units contemplated by the several companies, the Tuberculosis Control Division of the U. S. Public Health Service requested the National Electric Manufacturers Association to call a meeting of representatives of the X-ray industry for discussions on the subject. As a result of this meeting and of subsequent research, it was decided to standardize 70 mm. photofluorographic equipment as follows:

(*1*) The photofluorographic film should be of the blue-sensitive type.
(*2*) Photofluorographic screen should be of the blue-emitting type.
(*3*) Photofluorographic screen should be 15 x 17 inches in size.
(*4*) The distance from the X-ray tube to the photofluorographic screen should be 40 inches.
(*5*) The X-ray tube shift for stereoscopy should be 2.5 inches.
(*6*) The distance between the centres of successive exposures on the 70 mm. film-roll should be 3.25 inches.

SUMARIO

Durante el año pasado han aumentado decididamente las instalaciones roentgenográficas destinadas ex-profeso al hallazgo de casos tuberculosos. En tanto que antes sólo dos compañías producían aparatos fotorroentgenográficos en los Estados Unidos, hoy día hay seis.

Tratando de uniformizar los diseños fundamentales de los varios aparatos fotorroentgenográficos proyectados por las varias compañías, la División de Lucha Antituberculosa del Servicio de Sanidad Pública de Estados Unidos pidió a la Asociación Nacional de Fabricantes de Aparatos Eléctricos que convocara una reunión de representantes de la industria roentgenográfica para discutir este punto. A consecuencia de esta reunión y de los estudios sub-

siguientes, se decidió uniformizar el equipo fotorroentgenográfico de 70 mm en esta forma:

(*1*) La película roentgenográfica debe ser del tipo azul-sensible.
(*2*) La pantalla roentgenográfica debe ser del tipo azul-emisor.
(*3*) La pantalla fotorroentgenográfica debe medir 37.5 x 42.5 cm.
(*4*) La distancia del tubo roentgenográfico a la pantalla debe ser de un metro.
(*5*) La desviación del tubo roentgenográfico para la esteroscopía debe ser de 6.25 cm.; y
(*6*) La distancia entre los centros de las exposiciones sucesivas en el rollo de películas de 70 mm debe ser de 8.125 cm.

REFERENCE

(1) KURTZ, H. F.: Orthostereoscopy, J. Optic. Soc. America, 1937, *27*, 323.

APICAL LOCALIZATION OF PHTHISIS[1]

Its Significance in Treatment by Prolonged Rest in Bed

WILLIAM DOCK

No discussion of human tuberculosis and its management is complete or convincing unless it takes into account the fact that, in its inception and throughout much of its course, phthisis in adults is confined to the cephalad third of the lungs. Most members of white and many members of yellow racial groups are almost immune to tuberculosis except in this region. They pass through primary infections of the lung, of the upper respiratory tract and cervical nodes, or gut and mesenteric nodes with few or no symptoms in the vast majority of instances. But within a few months or after some years active lesions appear near the apices. Many of these also heal without causing symptoms or receiving treatment, but from the progressive apical lesions come the morbidity and mortality which make tuberculosis the most serious disease of early adult life. It is a remarkable fact that, even after the sputum and gastric washings contain bacilli at all times, pulmonary lesions for years may be limited to the cephalad third of the lungs.

Explanations of this curious predilection for the apex have been most unsatisfactory. Rich (1), after reviewing them, finds none convincing, and offers none of his own. Earlier reviews and proponents of theories based on habitus or presumed apical hyperventilation (2, 3) have been ignored by most clinicians. Those who have most consistently and convincingly urged bed-rest for the treatment of phthisis seem wholly unconcerned with the apical localization and its significance to pathological physiology and therapy.

The relation of man's erect posture to apical localization is usually ignored and has rarely been stressed. However, recent quantitative data (4) on the pressure in the right ventricles of human subjects have made it obvious that the effective arterial pressure in the cephalad third of the lungs is almost nil when an adult is in the erect posture. At such times the apical parts of the lungs have practically no pulmonic arterial inflow, and certainly no formation of tissue fluid or lymph. This must be of great significance in resistance to disease, and justifies a reëxamination of the problem of localization in the adult type of tuberculosis.

The systolic pressure in the normal man's right ventricle is 20 to 25 mm. Hg; the diastolic is approximately zero (4). As the intrathoracic pressure is about −5 mm. Hg, this means that the effective pulmonic arterial pressure is 25 to 30 systolic, 5 to 7 diastolic, with an average mean pressure of 15 to 18 mm. Hg. A column of blood 19 to 23 cm. high exerts an equal pressure and, as the apex of the lung is 15 to 30 cm. cephalad to the centre of mass of the right ventricular cavity, the pulmonic arterial pressure in the upper 5 cm. of the lung, even in systole, rarely can be more than 10 mm. Hg.[2] In tall, long-chested persons it will

[1] From the Department of Medicine, Long Island College of Medicine, Brooklyn, New York.

[2] It is now known that diastolic pressure in the pulmonic artery of man normally is 8 to 12 mm. Hg, mean effective pressure in the pulmonic arch 12 to 16 mm. Hg when recumbent. Effective pressure is not related to intrathoracic but to atmospheric pressure, as the intrapulmonic pressure fluctuates above and below this level.

be close to zero; the mean pressure in the latter group will be negative. Since it requires nearly 15 mm. Hg pressure to overcome the difference in colloidal osmotic pressure between the plasma and the pulmonary tissue fluid (5), no tissue fluid or lymph will be produced by filtration in the cephalad parts of the lungs of most adults while they are in the erect posture. Also, the flow of arterial blood will fall to zero, or at best to a small fraction of that at the lung bases. As the vessel walls are not rigid, the column of blood in the veins cannot act as a siphon.

As a result of the decreased flow, addition of carbon dioxide to and removal of oxygen from alveoli in this region will be minimal, and the alveolar gas tension will be more like that in the trachea than elsewhere in the lung, even if ventilation is minimal. Tubercle bacilli reaching this tissue will be in an optimal atmosphere to support their metabolism. This is probably not an important factor in apical localization, since the gas tension in most of the alveoli, or in highly arterialized organs like the kidneys, is quite adequate for luxuriant growth of *M. tuberculosis.*

As long as the subject is sitting or standing, the pulmonary arteries can bring few antibodies to the apical region. Even in inflamed tissue with increased vascular permeability, tissue fluid formation depends on adequate intravascular pressure. When pulmonary arterial pressure is practically zero, removal of bacterial products by lymph, or dilution by diffusion into the blood will be almost nil. Only when the patient is recumbent will these tissues be protected from accumulation of toxic substances. Removal of bacteria to the lymph nodes will be suspended during most of the waking hours, as will the replacement of antibodies and of monocytes from the blood.

In view of these facts, it is not remarkable that active tuberculosis so regularly begins in this region, or that it shows a predilection for the tall, long-chested individual and the lively young people who get a minimum of sleep. During their six or seven hours of recumbency the defenses of the body come into play and the gas tension becomes less favorable for the bacilli; at all other times the bacilli lodged near the apices of the lungs are in an ideal environment and the protective mechanism is fully inhibited, save for local cellular immunity.

Cournand and his coworkers (4), measuring the right ventricular pressure, observed that in patients with mitral stenosis, and in cases of left ventricular failure, the pulmonary arterial pressure rose to 80 or more mm. Hg during systole, with a significant rise in the diastolic pressures as well. Under such conditions, the blood flow in the apical parts of the lung, even in the erect position, would approximate that in other parts and the intravascular pressure would be high enough to form tissue fluid and lymph at all times. In such cases there is no longer the state of affairs which appears to account for the normal predisposition to apical and subapical tuberculosis. Pathological and clinical experience has everywhere proved that in such cardiac patients, in spite of wasting and of poor environment, the classical adult tuberculosis at the apices is almost unknown (6).

On the other hand, in cyanotic congenital heart disease there is overventilation of the lungs as a result of high arterial carbon dioxide tension and low oxygen tension and there is low pulmonary arterial pressure as a result of stenosis of the

pulmonary conus. When in the erect posture such patients have the highest oxygen tension in the cephalic parts of the lungs, and the lowest pulmonary arterial pressures cephalad to the heart of any group of people known to physicians. In pulmonic stenosis, the incidence of active tuberculosis is as high as 80 per cent in some series of adults, and averages about 20 per cent in the reported cases (7). This is far higher than in adults with normal circulatory function.

The statistics on these relationships of pulmonary tuberculosis and heart disease have been reviewed by White (6). The incidence of tuberculosis in mitral stenosis is reported as less than 4 per thousand cases, and the incidence of mitral stenosis in pulmonary tuberculosis at 5 per hundred thousand cases. White comments: "In contrast to the rarity of pulmonary tuberculosis in cases of pronounced mitral stenosis, it is said to be rather a usual development in congenital stenosis of the pulmonary orifice. In this regard it is of interest that just the opposite conditions exist in the pulmonary circulation with these two lesions: in mitral stenosis the pulmonary circulation is engorged and in pulmonary stenosis it is depleted."

Certain other facts deserve comment. In miliary tuberculosis the lesions often are considerably larger in the upper than in the basal third of the lungs (1) and this is most often noted in patients who were ambulatory in the early part of the disease and orthopneic during the final phase. It is less often seen in the terminal miliary lesions of patients long prostrated by phthisis. The large apical miliary lesions, and apical localization of reinfection, may occur in children over 7 or 8 years of age (1), but as we have no data on the pulmonic arterial pressure in childhood, and none on whether this localization occurs only in children who were continuously erect for twelve or more hours a day, it is not possible to say whether the same factors operated in these cases as in adults. Since systemic arterial pressure is low in childhood, it is possible that the same relation between the weight of the column of blood from apex to right ventricle and pressure in the right ventricle occurs in some children as in adults, when they are erect.

When tuberculosis does not promptly heal in the primary complex but spreads in a rapidly fatal form, it seems safe to assume that the individual (rarely a white adult, occasionally a child, often a Negro, American Indian, or South Sea Islander) does not develop immunity to the disease. Under these circumstances neither apical localization nor rapid growth near the apex is to be expected, since the absence of blood flow when erect cannot deprive this tissue of the protection which, in the cases previously considered, so effectively prevents or retards growth of lesions in the basal two-thirds of the lung. Only when poor blood flow removes protection can apical localization manifest itself, and this apparently cannot occur in those with minimal resistance and failure to heal the primary focus. The fact has long been recognized that apical disease is rare in populations into which tuberculosis has been introduced only recently, and that in these people the primary lesion progresses rapidly, and spreads through the lung in pneumonic forms.

The higher incidence of right apical lesions as contrasted with those on the left is readily accounted for by the theory given above, and by the anatomy of

the pulmonary arterial system. Blood gushing from the conus is directed toward the left apex, it passes through a large short left pulmonary artery which breaks into lobar branches within the left lung. But the right pulmonary artery is long, narrower than the left, and winds around the aorta. It breaks into lobar branches at some distance before reaching the hilum of the right lung. As it comes off the main branch at an angle, the blood following its tortuous course loses kinetic energy, and pressure therefore must be somewhat lower in the cephalad branches of the right pulmonary artery than in the same branch of the left. The bloodless zone therefore will extend a centimeter or more caudad on the right than on the left, and as the apices are cone-shaped this will add a relatively large mass of tissue in which the defenses are poor whenever the patient is erect. These anatomical relationships are shown in figure 1.

The indisputable facts, then, are that apical or subapical lesions may occur in patients who have and who maintain a high degree of immunity to progressive lesions anywhere else in the lungs or body; that the incidence is higher in those with long chests than in those with broad chests, in those with low pulmonic arterial pressure than in those with pulmonic hypertension; and that the pulmonary arterial pressure in those who develop the disease is such that very low pulmonic arterial blood flow and no formation of plasma filtrate and lymph can occur in the upper third of the lungs while the subject is erect. Long hours of activity and few hours of recumbency may not predispose the basal parts of the lungs to tuberculosis of a progressive type, but they do predispose to apical activity. Therefore, the lack of rest can only be important in that it gives the bacilli the maximal number of hours of optimal growth conditions and the tissues the minimal number of hours when the neutralization and dilution of toxic products, and the supply of antibodies and blood-borne phagocytes, are as adequate at the apices as elsewhere in the lungs.

The great frequency of silicotic lesions at the apex (8) also may be due to the fact that dust particles reaching this region will be removed by phagocytes less rapidly, and the injurious substances will be diluted and removed more slowly than in other parts of the lung. Hence scar tissue formation and its attendant acceleration of silicotic accumulation will be greatest in the apices, which are so nearly bloodless for fourteen to eighteen hours each day. This regional silicosis may also favor the development of tuberculosis.

Even with the earlier occurrence of silicosis and with the lack of protection of the apices when the immune subject is erect, healing without any therapy takes place in a very high percentage of apical lesions. This may be due either to the subject's taking more rest, or developing a higher level of immunity. The latter probably is the case in many instances, since the lesion is subjected to the immune mechanism for part of every day. This spontaneous healing of most apical lesions, as of nearly all primary lesions, shows how slight is the pathogenicity of this organism in most humans whose ancestors have been exposed to urban life for many generations. When supposedly immune persons develop active lesions in the lower two-thirds of the lung, spontaneous healing is less likely than with apical lesions. The mere fact that the lesion developed in the normally pro-

tected zone indicates that the entire protective mechanism has been disturbed. These are the lesions which progress in spite of adequate bed-rest, diet and general care.

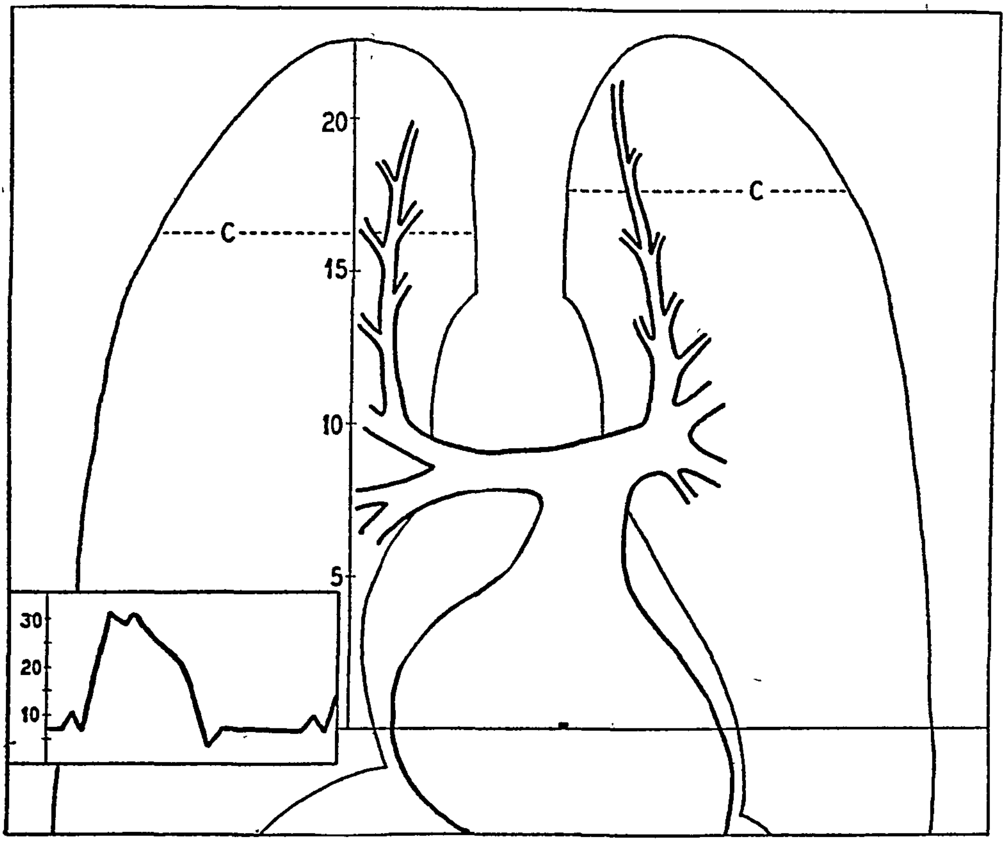


FIG. 1. This diagram is based on a chest film of a tall tuberculous patient, on anatomical charts (12) and the insert on curves of human intracardiac pressure (4).

It shows the relation of the column of blood in the pulmonary arteries to the right ventricle, and C indicates the level above which pulmonary blood flow cannot be maintained when the subject is erect, since the weight of the blood exceeds mean pulmonary arterial pressure. This level is lower on the right because the right pulmonary artery is long, tortuous and comes off at an acute angle from the blood-stream in the conus. Since there is a considerable fall in pressure between the main vessels and the capillaries, C actually must be lower in such tall subjects and lies at about this level in those of less than average height. Numerals indicate cm. above centre of right ventricle, and, in the insert, pressure in cm. H_2O above the intrapleural level.

If, as seems necessary from the foregoing facts, one assumes a steady accumulation of tubercle toxins about foci in the well aerated but bloodless apices of erect adults, it is obvious that the maximal daily concentration of these injurious substances will depend on the number of consecutive hours the subject remains erect. Half an hour or an hour of recumbency perhaps would lower the toxin level to that occurring about similar foci of bacilli in the lower two-thirds of the

lungs. The highest toxin level occurring each day might therefore be cut in half by a midday rest period, and in many people where the balance between resistance and susceptibility is so narrow this could easily make the difference between progress and regression of a lesion.

This explanation of apical susceptibility is therefore not a matter of academic interest. If it is correct, obviously the ideal treatment of the early apical lesion is complete recumbency for most of the twenty-four hours. Ulceration or intense peribronchial inflammation causes an extensive hyperplasia of the bronchial arterial system (9), thus giving the tissues affected a blood supply which no longer is significantly reduced by the erect posture, since the mean systemic pressure is nearly ten times that in the pulmonary arteries. In areas thus vascularized, progress of the lesions may be halted even though the disease is still spreading into adjacent normal areas, or at the opposite apex. Only constant recumbency, or a very marked rise in pulmonic pressure can restore to the apical third of the lung the same level of protection and resistance existing in the rest of the lung of the previously infected Occidental adult. Collapse therapy tends to bring the apex down to the level of the heart and prevents its aeration, so that recumbency will not be so important for the collapsed area or for one vascularized by the bronchial artery. It will, however, tend to limit spread into adjacent alveoli. With unilateral lesions, recumbency on the affected side should be favored. In any case, propping the patient up in bed should be regarded as interference with correct postural management. The tuberculous patient is not at "complete bed-rest" if he is allowed to sit up in bed for more than half an hour at a time.

The value of bed-rest in management of tuberculosis is generally accepted (10), as also the value of midday rest in preventing relapses. The value of confinement of afebrile patients to bed for twenty-four hours a day is by no means proved. It is quite possible that if the patient were allowed up, when he felt strong enough, for ten to thirty minutes four or five times a day, his morale and physical strength would be better preserved or more quickly restored. Even if this were permitted in the mornings when the afternoon temperatures were elevated, it might do more good than harm. As lesions regressed, the time up might be steadily lengthened—thirty minutes out of every two hours, one hour out of three, every other hour, finally one hour's rest after lunch and supper, and perhaps one hour after lunch or before supper and an average of nine hours at night for several years after all activity had ceased.

So long as bed-rest is only an empirical and nonspecific form of therapy, it is difficult to enforce it on intelligent people who feel well. On the other hand, an intelligible and simple physiological explanation of the factors which appear to predispose the apices to progressive disease will make coöperation more certain. In pulmonic stenosis, recumbency for one out of every four hours might be a reasonable prophylactic measure in adult cases which cannot be corrected by surgical procedures (11). To every adult with an apical lesion the hazards of the erect posture and the value of recumbency should be stressed. Yet twenty-four hours a day of complete bed-rest, with its attendant discomfort and higher

cost of nursing care, may not be superior to many hours of recumbency with brief periods out of bed.

Pratt (10), I think correctly, emphasizes out-of-door bed-rest as more effective than indoor resting. Out-of-doors, patients find reading less pleasant, because of wind and glare, and they also are more content to lie quiet. The wind and glare make dozing, sleeping and contemplation more agreeable, and they also stimulate the appetite, and perhaps muscular and vascular tone. All of this is undoubtedly of value, especially before the progress of the disease has been arrested and healing is clearly under way. But even earlier it may be safe to let the patient up and about for a few minutes several times a day, which makes alternate periods of bed-rest much more agreeable. In any event, relaxation will come more quickly if the bed is in the open and the patient is not propped up on pillows. It is being out-of-doors in the daytime that is of value, not being out at night, when an open window is quite as effective. Prolonged bed-rest will be better borne and can be more widely used if numerous and gradually lengthening periods of sitting up or strolling about can be alternated with recumbency. A consideration of the pathogenesis of the apical and subapical lesions suggests that this may be sound practice in patients not prostrated by disease.

SUMMARY

The juxta-apical pulmonary localization of tuberculous lesions in adults is believed to be explained by the low level of pulmonary arterial pressure and the height of the column of blood from right ventricle to apex when adults are erect. As a result the apex has little or no blood flow and the normal defense mechanism is inhibited during the waking hours. This theory is confirmed by the very low incidence of pulmonary tuberculosis in mitral stenosis, with its high pulmonic arterial pressure, and the very high incidence in congenital pulmonic arterial stenosis, with resultant low pulmonic pressures.

A sequel of this theory is that the recumbent posture brings resistance to tuberculosis in the apical regions to the same level as that elsewhere in the lungs. It is apparent that most Occidental adults have massive immunity to active tuberculosis except near the apices, and that recumbency should restore the protection in this region also.

It is the erect posture, maintained for many consecutive hours, which has given man an "Achilles' heel" through which the acid-fast arrow may pass. Either the pulmonary hypertension of mitral stenosis, or complete recumbency, corrects the physiological fault and makes the apical region as resistant as all others.

Restriction to bed is therefore not enough in the management of pulmonary tuberculosis. Recumbency, rather than rest in the conventional sense, appears to be essential to restore to the upper part of the lungs the resistance to tuberculosis which is so effective in preventing spread into the lower two-thirds of the lung. Sitting up in bed therefore reduces the effectiveness of the rest treatment. Brief periods of erect posture, which make eating, bathing and elimination more

agreeable, and reduce the cost of nursing care, probably are far less injurious than being propped up in bed for an hour or more at a time. Such brief periods of activity help to maintain morale, as well as muscular and vasomotor tone, and make it possible to continue the program of recumbency for the long periods of time which experience has proved necessary.

SUMARIO

La localización yuxta-apexiana de las lesiones tuberculosas en el pulmón de los adultos, parece deberse a la hipotensión arteriopulmonar y a la altura de la columna de sangre que va del ventrículo derecho al vértice cuando los adultos toman la posición erecta. Consecuencia de esto es que la circulación en el vértice es escasa o nula y el mecanismo normal de defensa queda inhibido durante las horas de vigilia. Confirman esta teoría, la bajísima incidencia de la tuberculosis pulmonar en la estenosis mitral con su hipertensión neumoarterial, y la altísima en la estenosis arteriopulmonar congénita con su hipotensión pulmonar.

Secuela de esta teoría es que la postura tendida eleva la resistencia a la tuberculosis en la región del vértice al mismo nivel que la de las otras partes de los pulmones. Es aparente que la mayor parte de los occidentales adultos poseen inmunidad masiva a la tuberculosis activa, salvo cerca de los vértices y que el decúbito debe restablecer también la protección en dicha región.

La postura erguida mantenida por muchas horas consecutivas, es la que ha dado al hombre el "talón de Aquiles" que puede atravesar el dardo ácido-rresistente. La hipertensión pulmonar de la estenosis mitral, o la postura completamente tendida, corrigen la falta fisiológica y dotan a la región del vértice de tanta resistencia como a las demás del cuerpo.

No basta pues, con el encamamiento para el tratamiento de *la tuberculosis* pulmonar. El acostamiento, más bien que el descanso en el sentido convencional, parece ser esencial para devolver a la porción superior de los pulmones la resistencia a la tuberculosis que es tan eficaz para prevenir la difusión a los dos tercios inferiores del pulmón. La posición sedente en cama rebaja la efectividad del reposo terapéutico. Los breves períodos de postura erecta que hacen más agradables la comida, el baño y la eliminación y reducen el costo de la asistencia de enfermería, resultan probablemente menos perjudiciales que el sentarse en cama apoyado por una hora o más cada vez. Esos breves períodos de actividad ayudan a mantener la moral, así como la tonicidad muscular y vasomotriz y permiten continuar el plan del acostamiento durante los largos períodos que la experiencia ha demostrado ser necesarios.

REFERENCES

(1) Rich, A.: The problem of apical site of origin of adult type pulmonary tuberculosis in The Pathogenesis of Tuberculosis, Charles C Thomas, 1944, p. 768.

(2) Neumann, W.: Über die mechanischen Ursachen der Disposition der Lungenspitzen zur tuberkulösen Phthise, Beitr. z. Klin. d. Tuberk., 1919, *40*, 1.

(3) Loeschke, H. and Dehoff, E.: Pathologische Anatomie der Lungenspitzentuberkulose, Ergebn. d. ges. Tuberk.-Forsch., 1931, *2*, 81.

(4) Cournand, A., *et al.*: Recording right heart pressures in man, Proc. Soc. Exper. Biol. & Med., 1944, *55*, 34.

(5) Drinker, C. K., and Yoffey, J. M.: Lymphatics, Lymph, and Lymphoid Tissue, Harvard University Press, 1941, pp. 84–88.

(6) White, P. D.: Heart Disease, Macmillan Co., 1944, p. 398.

(7) Auerbach, O., and Stemmerman, M. G.: The development of pulmonary tuberculosis in congenital heart disease, Am. J. M. Sc., 1944, *207*, 219.

(8) Davson, J., and Susman, B: Apical scars and their relationship to siliceous dust accumulation in non-silicotic lungs, J. Path. & Bact., 1937, *45*, 597.

Davson, J.: The early stages of apical scar development, J. Path. & Bact., 1939, *49*, 483.

(9) Wood, D. A., and Miller, M.: The rôle of the dual pulmonary circulation in various pathologic conditions of the lungs, J. Thoracic Surg., 1938, *7*, 649.

(10) Pratt, J. H.: The evolution of rest treatment of pulmonary tuberculosis, Am. Rev. Tuberc., 1944, *50*, 185.

(11) Blalock, A., and Taussig, H. B.: Surgical treatment of malformations of the heart, J. A. M. A., 1945, *128*, 189.

(12) Grant, J. C. B.: Atlas of Anatomy, Williams & Wilkins, Baltimore, 1943, pp. 240, 250, 266.

PULMONARY FUNCTION TESTS[1,2]

A Discussion of Ventilatory Tests. A Description of a Method for Measuring the Diffusion of Oxygen and Carbon Dioxide in the Lungs

GEORGE G. ORNSTEIN, MYRON HERMAN, MARCELLA W. FRIEDMAN AND ERNEST FRIEDLANDER

Pulmonary function should be judged both by measuring the ventilatory capacity of the lungs and the permeability of the alveolar components of the lungs to the diffusion of oxygen and carbon dioxide. A good deal of attention has been directed to the ventilatory phase of lung function and too little to the diffusion of gases in the lung tissues (alveolar membrane and capillaries).

Before discussing the above factors in pulmonary dysfunction we wish to state a series of conditions which may impair pulmonary function.

1: Intrinsic diseases of the lung due to the effect of the toxemia caused by infection.
2: Pollution of the general circulation by venous blood flowing through unaerated lung tissue. (Early phases of massive collapse of the lung, atelectasis, lung hepatization.)
3: Both acute and chronic inflammatory changes affecting the lining of the alveoli and the lung capillary system. (Impairment of permeability of the alveolar component of the lung.)
4: Blood changes as in chronic anemia.
5: Overdistention of the alveoli with thinning out of the alveolar walls. The capillaries are overstretched and constricted.
6: Congestion of the lung tissues due to cardiac failure (impairment of permeability besides marked decrease in ventilatory capacity).
7: Cellular poisoning as in cyanide poisoning. (Histotoxic anoxia.)

Thus, we have other factors not associated with ventilation and permeability which affect pulmonary function (1, 2, 4 and 7 above).

Dyspnea and anoxia result when either or both the ventilatory or the lung permeability functions are disturbed to such an extent that the normal gaseous exchanges cannot be accomplished. The term dyspnea implies difficulty in breathing and anoxia, the failure of the tissues to receive an adequate supply of oxygen. When dyspnea and anoxia exist in the true sense of their definitions, there is no need of any tests for their recognition. However, early departures from normal interchanges of gases are difficult to recognize whether due to ventilatory or permeability changes. Dyspnea and anoxia only occur (when easily recognized) when both ventilatory and permeability functions are greatly disturbed. It is at this stage that oxygen and carbon dioxide changes in the blood are indicative of anoxia.

Most pulmonary function tests have been ventilatory measurements. The diffusion of gases has also been discussed but few methods have been of value.

[1] From the New York Medical College and Metropolitan Hospital Research Unit, Dr. Thomas H. McGavack, Director, New York, New York.

[2] This research project was supported by a contribution by Mr. Joe Lowe and Mr. Louis Price.

As previously mentioned, a decrease in arterial oxygen saturation below normal limits occurs more in the late stages of pulmonary dysfunction.

Humans at basal conditions are usually comfortable with just their minute resting ventilation. Thus at basal conditions the resting minute volume of air diffuses an adequate supply of oxygen to the tissues of the body and equally eliminates the excess carbon dioxide. Therefore, pulmonary permeability tests concerning diffusion of oxygen and carbon dioxide are of little value under basal conditions in early states of pulmonary dysfunction.

There has been some casual observations concerning poor permeability of gases in lungs. Siebeck (1) in 1912 observed that, when cardiac patients were made to inspire pure hydrogen, the expired air in the dyspneic, decompensated patients contained a higher percentage of the inspired hydrogen than it did in compensated cardiac patients or in normal persons used as controls. Peabody *et al.* (2) found the consumption of oxygen and the production of carbon dioxide greater in the compensated cardiac patient and the consumption of oxygen less and the production of carbon dioxide less in the decompensated cardiac patient. Peabody's group made the above observations in a study of the basal metabolism and the minute volume of respiration of patients with cardiac disease.

Thus from the above discussion pulmonary function is to be judged by three distinct factors.

1: Ventilatory capacity.
2: Diffusion of oxygen and carbon dioxide, in the alveolar component of the lung. (Permeability.)
3: Extraneous factors.
   a. Pollution of general circulation.
   b. Toxemia.
   c. Red cell changes in the blood (anemia).
   d. Changes in the hemoglobin (carbon monoxide poisoning).
   e. Histotoxic anoxia.

In this discussion the extraneous factors may be dismissed for they are easily recognized and we therefore will discuss the ventilatory and diffusion factors.

VENTILATORY TESTS

(*1*) The simplest ventilatory test is the measuring of the vital capacity[3] by means of a spirometer and comparing the results obtained with the calculated vital capacity[4] from charts based on the standing height standard, the surface area standard and the weight standard.

Knowing the actual vital capacity and the calculated normal vital capacity, the maximum minute ventilation of the subject on maximum effort may be predicted. Sturgis *et al.* (3) have studied the actual minute ventilation in a group of 12 young normal men. They found that these young normal men had a maxi-

[3] The actual vital capacity will be indicated by A.V.C.

[4] The calculated normal vital capacity per standard height, standard weight and sex will be indicated by C.N.V.C.

mum minute ventilation of twelve times the resting minute ventilation when they rode a stationary bicycle until they were forced to stop because of complete exhaustion. During the last one and a half minutes of the ride when the exercise was most violent and the dyspnea great, the average minute ventilation of air they breathed was 60.5 liters or about twelve times the amount of air they breathed when they were lying down and at complete rest. Sturgis and his group also noted, when the maximum minute ventilation was reduced to six times the resting minute ventilation, the 12 young men could walk on level ground without any dyspnea. With this reduction in the minute ventilation, any effort of exertion, such as climbing stairs, induced symptoms of dyspnea. The dyspnea further increased as the maximum minute ventilation was decreased. Sturgis *et al.* worked out a formula to predict the maximum minute ventilation which was sufficiently close to the actual results obtained in their experiments. The formula is as follows:

$$\frac{\text{Actual vital capacity} \times 35}{3} = \text{Predicted maximum minute ventilation at maximum exertion}$$

In the above formula 35 represents the average respiratory rate during the last one and a half minutes of violent exercise. The numeral 3, the denominator, represents the depth of inspiration as being one-third of the vital capacity through this last one and a half minutes of violent exercise.

Kaltreider and McCann (4) confirmed the above observations of Sturgis and his coworkers. The former investigators present a formula which they state is closer to the actual maximum minute ventilation. The Kaltreider and McCann formula is as follows:

$$\frac{41 \times \text{actual vital capacity} \times 37}{100} = \text{Predicted maximum minute ventilation at maximum exertion}$$

Ornstein and Epstein (5) worked out a formula utilizing the actual vital capacity and calculated normal vital capacity of the subject based on the investigation of Sturgis *et al.* and Kaltreider and McCann, which also predicted the maximum minute ventilation on maximum exertion. Ornstein and Epstein assumed that the average normal person's maximum minute ventilation on maximum exertion was ten times the resting minute ventilation. The formula is as follows:

> Maximum minute ventilation on maximum exertion based on actual vital capacity:X::Maximum minute ventilation on maximum exertion based on calculated normal vital capacity : 10

X equals the number of times the maximum minute ventilation on maximum effort is greater than the resting minute ventilation. The formula may be reduced simply to:

$$\frac{\text{Actual vital capacity} \times 10}{\text{Calculated normal vital capacity}} = \text{The number of times the maximum minute ventilation on maximum exertion is greater than the resting minute ventilation}$$

Using the above formula, Ornstein and Epstein found they could predict the symptoms of dyspnea in 392 patients examined. They found that when the predicted maximum minute ventilation on maximum exertion was no lower than six times the resting minute ventilation there were no symptoms of dyspnea, except when there was exertion comparable to the climbing of stairs. They also noted that, below the above level, symptoms of dyspnea increased proportionally.

(2) Maximum breathing capacity is another means of measuring ventilatory capacity. This method of estimating lung ventilation was presented by Hermannsen (6). The subject, connected to a spirometer, was allowed to breathe normally for a few minutes to become adjusted to the new condition of breathing and then was made to breathe at maximum capacity as deeply and rapidly as possible for thirty seconds. The maximum breathing capacity was recorded on a moving drum.

We did not record the maximum breathing capacity by using a moving drum. We used a Tissot spirometer. A Douglas bag could also be used and the gas accumulated measured through a gasometer. We used the standards set up by Cournand, Richards and Darling (7) for our normal measurements. They gave as the mean values for males 154 liters per minute; for females 100 liters per minute.

Cournand and Richards utilized the maximum breathing capacity and subtracted from this value the resting minute ventilation, thus arriving at a factor which they call the breathing reserve. This latter figure is multiplied by 100 and divided by the maximum breathing capacity. The result is labelled the percentage of the breathing reserve. An example of this is as follows:

$$\frac{\text{Breathing reserve (145)}}{\text{Maximum breathing capacity (150)}} \times 100 = \text{96.6 per cent (Percentage breathing reserve)}$$

The above authors state that the threshold of dyspnea is reached when the percentage breathing reserve ranged from 60 to 70 per cent.

In another investigation they could determine from the percentage breathing reserve of the patient at rest how the individual would react to exercise, as far as dyspnea was concerned. The following are their conclusions:

Above 93 per cent breathing reserve, no dyspnea.
Between 92 and 87 per cent, half of the persons were not dyspneic. The remaining half of the cases were dyspneic for less than two minutes after exercise.
Between 75 and 85 per cent, all were dyspneic up to two minutes.
Between 85 and 81 per cent, the subjects were either mildly or severely dyspneic.
Below 80 per cent, the dyspnea after exercise lasts at least two minutes.

We were impressed with the completeness of information which could be gleaned by simply dividing the resting minute ventilation into the maximum breathing capacity. The result is the actual number of times an individual could ventilate above that of his resting minute ventilation. This we have

called the "Ventilatory Reserve." The normals are 20 and 13 in males and females, respectively, and were obtained in the following manner:

> The average resting minute ventilation was found to be 7,500 cc.
> The average maximum breathing capacity (as determined by Cournand, Richards and Darling) was set at 154 liters for males and 100 liters for females.

$$\frac{\text{Males } 154{,}000 \text{ cc.}}{7{,}500 \text{ cc.}} = 20$$

$$\frac{\text{Females } 100{,}000 \text{ cc.}}{7{,}500 \text{ cc.}} = 13$$

It can be seen that the "Ventilatory Reserve" test is of extreme value since it is based on both the actual resting minute ventilation as well as the actual maximum breathing capacity. Variation in either one of these figures affects the end results.

The value of the "Ventilatory Reserve" test is best illustrated in the following patient with a far advanced bilateral pulmonary silicosis (figure 2). His A.V.C. was 1,900 cc. and C.N.V.C. was 3,700 cc. His predicted maximum minute ventilation per maximum exertion (Ornstein and Epstein) was 5.1 times his resting minute ventilation which indicated quite a decrease in pulmonary ventilation. The resting minute ventilation was 8,000 cc. and his maximum breathing capacity was 18,150 cc., which indicated a marked decrease in maximum breathing capacity (normal male 150,000 cc.). Cournand and Richards' modification of the maximum breathing capacity test was as follows:

$$\frac{18{,}150 - 8{,}000}{18{,}150} \times 100 = 55 \text{ per cent of Breathing reserve}$$

The authors' modification test:

$$\frac{\text{Maximum minute breathing capacity}}{\text{Resting minute ventilation}} = \begin{array}{l}\text{Reserve of ventilation times the resting minute ventilation} \\ \quad\text{(Normal male 20)} \\ \quad\text{(Normal female 13)}\end{array}$$

$$\frac{18{,}150}{8{,}000} = 2.02 \text{ Reserve ventilation (normal 20)}$$

All the ventilatory tests in the above case indicated a diminution in ventilatory capacity but the ventilatory reserve as measured by dividing the maximum minute breathing capacity by the resting minute ventilation was the most accurate. This patient gave evidence of dyspnea on the least exertion, though at basal conditions he could sleep in bed without a pillow.

The predicted maximum ventilation on maximum exertion (Ornstein and Epstein) and the Cournand and Richards modification of the maximum minute breathing capacity did not infer the marked dyspnea on exertion that existed. The authors believe the ventilatory reserve test based on dividing the resting

minute ventilation into the maximum minute breathing capacity was the best of the ventilatory tests because of its more accurate prediction.

PULMONARY DIFFUSION OF OXYGEN AND CARBON DIOXIDE

It has been shown above that, when the ventilatory function of the lung is reduced below 60 per cent of the calculated normal vital capacity, dyspnea appears on exertion. The dyspnea increases directly in proportion to further decreases in vital capacity. The authors have demonstrated this dyspnea in normal males by reducing the expansion of the thorax and the movements of the diaphragms by means of a canvas jacket (table 3).

We may conclude from the above that decreases in vital capacity affects pulmonary function. We noted the dyspnea varied in different patients with pulmonary disease with the same reduced vital capacities. We also noted symptoms of dyspnea on exertion in patients with pulmonary disease who had a sufficient ventilatory function of the lungs. We therefore concluded that the ventilatory effect was only one phase of pulmonary function and that in these cases the more important question was what happened to the oxygen once it reached the alveoli of the lungs.

The present tests for measuring the efficiency of alveolar permeability to oxygen and carbon dioxide are not sensitive enough to recognize changes except in the late stages of pulmonary dysfunction. Thus, the study of respiratory gases in arterial blood and the study of oxygen consumption and carbon dioxide elimination per liter of ventilation at basal conditions are not delicate enough to indicate early changes of lung permeability.

It occurred to the authors that normal subjects having good lungs should interchange oxygen and carbon dioxide more freely when connected with a rebreathing bag containing a known amount of oxygen and carbon dioxide, than another group of subjects having impaired lungs.

We planned a method of breathing in a rebreathing bag after the original method of Plesch (9) which he used in determining venous carbon dioxide. A rubber rebreathing bag was fitted to a three-way glass valve. The rubber mouth piece was attached to a tube which communicated with the room atmosphere. A turn of the three-way cock connected the tube with the rebreathing bag. There are two tubes opening into the tube leading to the rebreathing bag for the removal of gas samples. (See figure 1.)

The subject was made to rest for thirty minutes in a sitting position. The rebreathing bag was filled with 1,000 cc. of room air. The rebreathing bag was then attached to the subject by means of a rubber mouth piece. The nose was blocked by means of a nasal clip. The subject was allowed to breathe the room air through the open tube for a minute and the three-way cock was turned to connect the subject with the rebreathing bag. The cock was then turned at the end of an exhalation. After twenty seconds of breathing (the gases in the lungs then are *presumably* in equilibrium with the gases in the rebreathing bag) the cock was again turned to close off the rebreathing bag and connect the respiratory tract to the atmospheric air in the room.

The gases in the rebreathing bag were then withdrawn into gas sampling tubes after the small sampling connection was washed with the respired air. The gases in the sampling tubes were then analyzed for oxygen and carbon dioxide by means of a Haldane-Boothby-Sandiford gas analyzer.

At basal conditions we found so little variation in the oxygen and carbon dioxide percentages between subjects with apparently normal and abnormal lungs that we concluded the above test, under basal conditions, was of no value. Patients with just a little more reserve than their resting minute ventilation are able to supply an adequate amount of oxygen to their tissues and do not have symptoms of dyspnea and anoxia. Such symptoms only develop when the demand for oxygen is greater than their reserve. We therefore decided to change from basal conditions and to repeat the same rebreathing test after a "standard exercise." The "standard exercise" was the universal one in which the subject

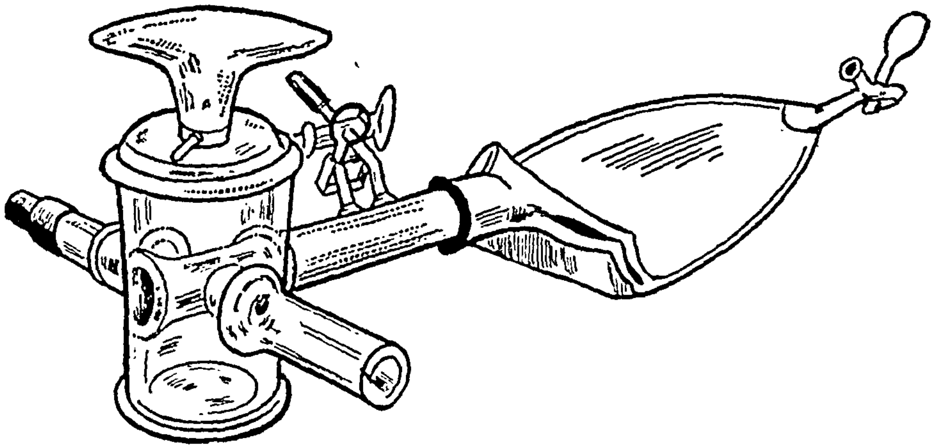


FIG. 1. A rubber rebreathing bag is fitted to one arm of a three-way glass tube. A rubber mouthpiece is attached to another arm. There are two connections leading from the rebreathing bag from which samples of gas can be removed.

walks up and down a foot stool, 20 cm. high, thirty times in one minute. The above exercise produces a demand for oxygen far in excess of the normal need under basal conditions.

With the introduction of the standard exercise the rebreathing tests showed distinct differences between the normal and impaired lung. The rebreathing test was carried out exactly the same as the test under basal conditions, described above. But, while breathing room air the subject was made to walk up and down a foot stool, 20 cm. high, thirty times a minute. In a few cases the subjects were not able to walk the stairs more than twenty-six to twenty-seven times and we considered that acceptable. At the end of the exercise period the subject was seated and the three-way cock turned at the end of an exhalation and connected with the rebreathing bag for twenty seconds of rebreathing. The air in the bag was then withdrawn into gas sampling tubes, after the small sampling connection was washed with the respired air and the gas was analyzed.

In a group of 23 males considered to have normal lungs, the average analysis of gases in the rebreathing bag, following the standard exercise described above, revealed the following changes from the room air previously present in the rebreathing bag: The mean oxygen volume percentage was 7.95 per cent instead of 20.9 per cent. The carbon dioxide volume rose to 8.09 per cent from 0.03 per cent. Table 1 reveals the details of the gas analysis in the 23 normal males.

A normal male will diffuse about 12.95 volume per cent of oxygen from a rebreathing bag containing room air in a period of twenty seconds after a minute

TABLE 1

Normal males

CASES	AGE	ACTUAL VITAL CAPACITY	VOLUME PERCENTAGES OF GASES IN REBREATHING BAG AFTER STANDARD EXERCISE	
			O_2	CO_2
1. F. W.	32	79%	9.50	8.12
2. W. F.	24	100%	9.48	7.24
3. W. W.	47	75%	9.13	7.12
4. W. H.	50	96%	9.07	8.28
5. W. P.	24	107%	8.85	7.77
6. G. O.	52	79%	8.84	7.90
7. B. Z.	23	110%	8.29	8.24
8. J. W.	27	88%	8.14	8.62
9. C. B.	27	113%	8.08	8.36
10. P. A.	37	79%	8.02	7.64
11. J. M.	23	80%	7.98	8.30
12. D. S.	25	122%	7.89	7.67
13. W. S.	23	105%	7.86	8.70
14. K.	59	89%	7.81	7.77
15. D. G.	23	102%	7.80	7.74
16. T. P.	24	100%	7.66	8.63
17. B. W.	25	110%	7.14	7.96
18. E. F.	38	94%	7.08	8.62
19. F. P.	36	78%	6.95	8.52
20. A. G.	36	91%	6.87	8.63
21. P. R.	26	88%	6.86	7.86
22. F. S.	28	112%	6.84	8.15
23. B. H.	25	100%	6.79	8.17

Average O_2 = 7.95%—Standard Deviation = ±.851.
Average CO_2 = 8.09%—Standard Deviation = ±.436.

of "standard exercise." The authors intend to use the volume percentage of the oxygen found in the rebreathing bag, after the exercise as the result of the test. The mean normal in the male will be: oxygen 7.95 volume per cent, carbon dioxide 8.09 volume per cent and nitrogen 83.96 volume per cent. Any increase in oxygen volume percentage will be considered to deviate from the normal diffusion of oxygen, though in obtaining our normal volume percentage, the highest was 9.50 per cent and the lowest was 6.79 per cent. The highest volume percentage of carbon dioxide was 8.70 per cent and the lowest was 7.12 per cent.

In 25 similar normal females (table 2) the average mean percentage of gases in the rebreathing bag after standard exercise was: oxygen 8.30 volume per cent, carbon dioxide 7.70 volume per cent and nitrogen 84.00 volume per cent. The average female diffused 12.6 per cent oxygen in the twenty seconds of rebreathing, compared to 12.95 volume per cent in the male. The volume percentage of oxygen and carbon dioxide can be seen in table 2.

TABLE 2

Normal females

CASES	AGE	ACTUAL VITAL CAPACITY	VOLUME PERCENTAGES OF GASES IN REBREATHING BAG AFTER STANDARD EXERCISE	
			O_2	CO_2
1. B. B.	19	93%	9.70	6.79
2. D. D.	23	100%	9.50	7.70
3. M. K.	24	106%	9.07	6.93
4. M. P.	18	100%	9.02	7.79
5. P. F.	17	106%	8.97	8.36
6. C. L.	22	107%	8.90	7.46
7. D. G.	20	110%	8.78	7.90
8. M. D.	18	88%	8.66	7.82
9. M. L.	25	104%	8.63	6.76
10. E. B.	20	111%	8.42	8.06
11. J. M.	18	120%	8.36	8.03
12. E. L.	21	100%	8.23	7.42
13. G. G.	18	96%	8.19	7.63
14. M. F.	31	94%	8.12	7.18
15. J. A.	20	110%	8.12	7.61
16. G. F.	19	85%	8.08	7.38
17. S. R.	18	100%	8.07	7.24
18. F. L.	43	81%	8.03	7.68
19. P. J.	17	93%	8.02	7.47
20. G. V.	23	103%	7.90	7.90
21. M. P.	25	120%	7.84	8.31
22. E. C.	42	91%	7.78	8.63
23. M. G.	20	103%	7.40	7.62
24. R. K.	21	72%	6.91	8.26
25. M. C.	22	100%	6.81	8.51

Average O_2 = 8.30%—Standard Deviation = ± .714.
Average CO_2 = 7.70%—Standard Deviation = ± .497.

It is interesting to note that, as the oxygen is absorbed from the rebreathing bag, it is replaced by both carbon dioxide and nitrogen. It was surprising to the authors to note the more rapid diffusion of nitrogen than was expected of a neutral gas.

Whether the above percentages of gases are dependent entirely on permeability of the alveolar capillary tissues of the lung or are also directly a result of pulmonary circulation and heart stroke will be discussed later. The test was limited to twenty seconds so that no blood which has been aerated in thelungs

will again return to the pulmonary circulation. (Henderson and Prince (10), Best and Taylor (11).)

The authors believed that, if the circulation played an important rôle in the changes of the diffusion of oxygen in the lung, it would be found out by artificially modifying the ventilation of the lung by hampering the excursion of the thorax and movements of the diaphragm. The decrease in the ventilatory mechanism would modify greatly the filling of the right auricle and ventricle with venous blood.

Eight normal males had their thoraces and abdomens strapped by means of a heavy canvas jacket so that the thoracic expansions and diaphragmatic excursions were limited in their movements (table 3). Before the canvas jacket was applied the A.V.C. was measured and the volume percentage noted compared to the C.N.V.C. A rebreathing test for twenty seconds after the standard exercise was done and the results noted. The subject was then put into the canvas jacket and strapped until the A.V.C. was reduced a considerable percentage. The same rebreathing test was then done and the results noted and compared to the findings before the vital capacity was reduced.

TABLE 3

Rebreathing bag test with standard exercise before and after restriction of vital capacity

CASES	NORMAL VITAL CAPACITY	VOLUME PERCENTAGES IN REBREATHING BAG AFTER STANDARD EXERCISE		REDUCED VITAL CAPACITY	VOLUME PERCENTAGES IN REBREATHING BAG AFTER STANDARD EXERCISE	
		O_2	CO_2		O_2	CO_2
1. G. O.	$\frac{\text{A.V.C. } 3.8}{\text{C.N.V.C. } 4.8}$ 79%	8.84	7.90	$\frac{1.9}{4.8}$ 40%	8.54	7.83
2. E. F.	$\frac{\text{A.V.C. } 4.1}{\text{C.N.V.C. } 4.4}$ 94%	8.62	7.08	$\frac{2.1}{4.4}$ 48%	8.35	7.31
3. W. P.	$\frac{\text{A.V.C. } 4.8}{\text{C.N.V.C. } 4.5}$ 107%	8.41	7.62	$\frac{2.3}{4.5}$ 50%	8.47	7.87
4. P. R.	$\frac{\text{A.V.C. } 4.0}{\text{C.N.V.C. } 4.6}$ 88%	6.86	7.86	$\frac{1.9}{4.6}$ 41%	7.66	7.83
5. P. S.	$\frac{\text{A.V.C. } 5.3}{\text{C.N.V.C. } 4.9}$ 108%	6.96	8.29	$\frac{2.1}{4.9}$ 43%	7.96	8.10
6. C. M.	$\frac{\text{A.V.C. } 3.2}{\text{C.N.V.C. } 4.6}$ 70%	9.42	7.72	$\frac{1.2}{4.6}$ 26%	9.08	7.54
7. R. L.	$\frac{\text{A.V.C. } 5.1}{\text{C.N.V.C. } 4.9}$ 104%	8.59	8.03	$\frac{1.9}{4.9}$ 39%	9.14	7.65
8. S. S.	$\frac{\text{A.V.C. } 4.5}{\text{C.N.V.C. } 4.4}$ 102%	7.80	8.13	$\frac{1.8}{4.4}$ 41%	8.30	7.60

The vital capacity was reduced in 8 normal males from 50 per cent to 26 per cent of the C.N.V.C. In all the 8, dyspnea was present on the least exertion and was proportional to the extent of the reduction in ventilatory function.

In spite of the reduction of vital capacity the diffusion of gases was not mate-

rially changed (table 3). In the subject where the vital capacity had been reduced from 70 to 25 per cent of the C.N.V.C. the oxygen was 9.42 per cent in the rebreathing bag after the standard exercise and 9.08 per cent after the vital capacity was reduced down to 25 per cent of the C.N.V.C. Thus, in a group of 8 males in whom the excursion of the thoracic wall and the diaphragms were definitely restricted enough to modify the inflow of venous blood to the right heart there were no significant changes in the volume percentage of oxygen and carbon dioxide in the rebreathing bag after standard exercise.

There is another factor that should be discussed at this time. Physiologists have looked upon the ventilation of lungs as comparable to the opening of a fan; some areas are more distended than others. The fully ventilated lung aerates the pulmonary arterial blood fully, whereas lung tissue not fully ventilated is oxygenated to a lesser extent. We wish to quote MacLeod (12). "It is important to remember that all portions of the lung do not open up equally on inspiration. When the tidal air is normal in volume this is of little consequence, but when it is reduced as in shallow breathing, the only alveoli which will be adequately ventilated will be those of the more expansile regions. The results of the shallow breathing will of course be that the blood leaving the well ventilated portions will be saturated with oxygen and have a relatively low carbon dioxide tension, whereas that from ill ventilated portions will be unsaturated with oxygen and overloaded with carbon dioxide." The experience with the 8 subjects previously cited does not bear out the above. There can be quite a disturbance of ventilation in a normal lung without material changes in oxygen and carbon dioxide diffusion taking place. The above experience also bears out our clinical impression that some patients with diminished ventilatory function may diffuse gases within the normal range and show less symptoms of dyspnea than other patients with the same diminished ventilatory changes, but who also have lungs less permeable to diffusion of oxygen.

Having established normal findings we then turned our attention to patients with impaired lungs.

PATIENTS WITH IMPAIRED LUNGS

Case H. S., a white male of 39 years, has a far advanced bilateral pulmonary silicosis (figure 2). His A.V.C. was 1,700 cc. and his C.N.V.C. was 3,700 cc. His A.V.C. was 45 per cent of his C.N.V.C. The patient was dyspneic at the least exertion.

A rebreathing bag test after the standard exercise was done. The analysis of the gases in the rebreathing bag was as follows: oxygen 11.8 volume per cent; carbon dioxide 6.92 volume per cent. H. S. utilized less oxygen than the normal control subjects and less carbon dioxide was found in the rebreathing bag than in normal control subjects. The rebreathing bag test was repeated a number of times with the oxygen and carbon dioxide volume per cent showing only minimal variations (table 4). H. S. showed less capability of the lungs to diffuse oxygen and carbon dioxide. Compared to the normal control male cases, the oxygen volume per cent and oxygen pressure were much higher, namely 11.8 volume per cent and 84.13 mm. Hg. pressure. In the average normal male the mean oxygen volume per cent is 7.95 and the pressure in mm. of Hg. 55.8. The difference in oxygen pressure between H. S. and the normal male gives a more graphic con-

cept of the ability of the lungs to oxygen diffusion than does the difference in volume percentage.

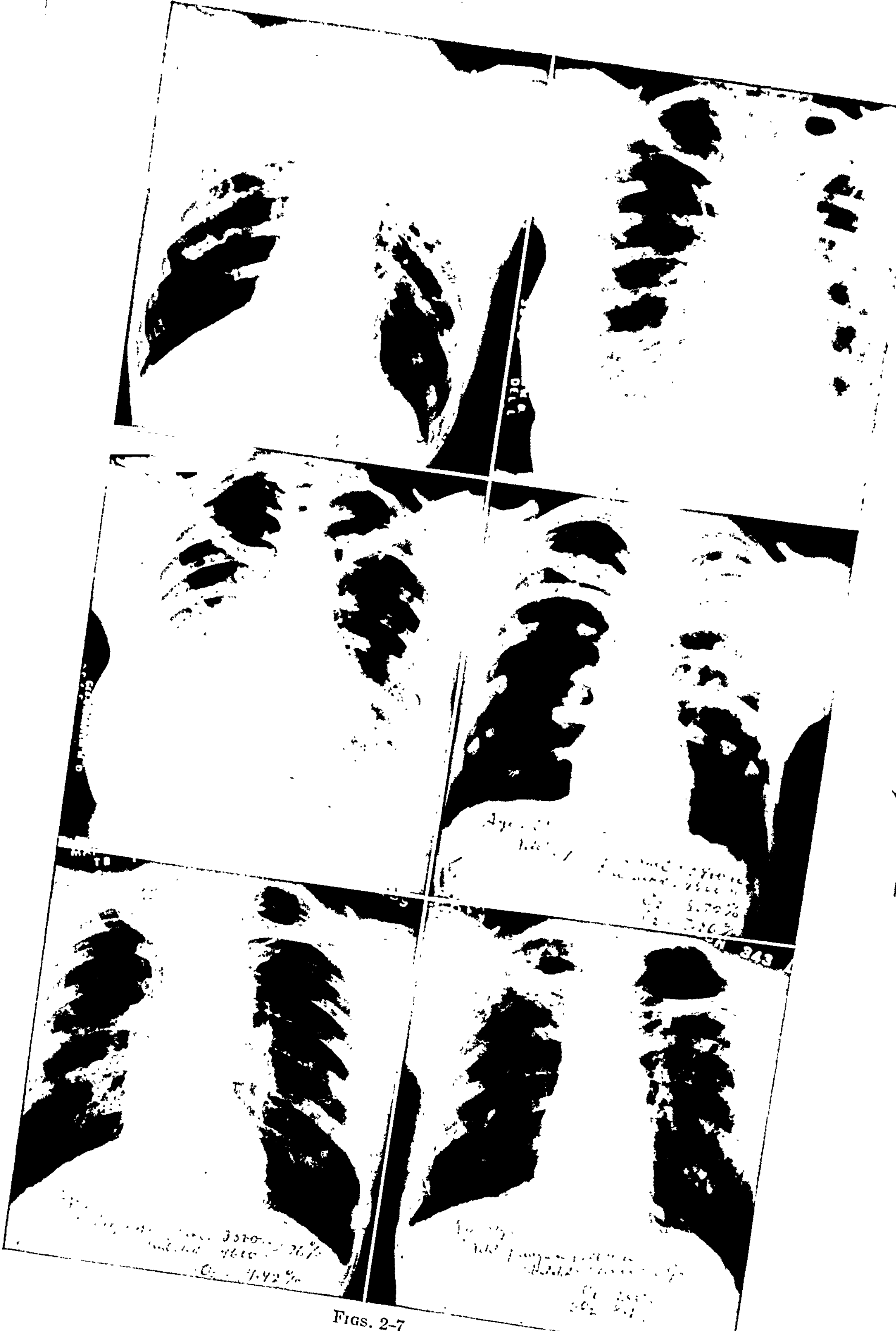
TABLE 4

Case H. S.- 39 years Far advanced silicosis of lungs (figure 2)
A.V.C. 1,700 cc., C.N.V.C. 3,700 cc. A.V.C. 45 per cent of C.N.V.C.

3-21-44	Alveolar Air		
	O_2 13.30%	CO_2 6.33%	
	O_2 13.80%	CO_2 6.18%	
	O_2 13.62%	CO_2 6.67%	
4-6-44	Rebreathing Test—basal conditions thirty-five seconds		
	O_2 13.29%	CO_2 6.15%	
4-10-44	Rebreathing Bag—standard exercise		
	O_2 11.86%	CO_2 7.52%	
5-31-44	Douglas Bag—one minute breathing		
	At Rest	*After Standard Exercise*	
	O_2 17.51%	O_2 17.13%	
	CO_2 3.23%	CO_2 3.48%	
6-19-44	Rebreathing Bag after standard exercise	Douglas Bag	
		At Rest	*After Exercise*
	O_2 11.80%	O_2 17.67%	O_2 17.27%
	CO_2 6.92%	CO_2 2.85%	CO_2 3.60%
3-2-45	Oxygen and Carbon Dioxide in Rebreathing Bag after standard exercise		
	O_2 11.92%		
	CO_2 6.90%		

A study was made of 170 patients with impaired lungs. The authors noted that the capability of the lungs to diffuse oxygen and carbon dioxide had no definite relationship to the ventilatory function of the lungs. Where the ventilatory function was normal, the diffusion of oxygen and carbon dioxide was also good and only occasionally was there poor diffusion in lungs with good ventilatory function. On the other hand, when the ventilatory function of the lungs was much reduced, the diffusion of oxygen and carbon dioxide had no relationship to the ventilatory reduction.

The authors also noted that the roentgenogram is of limited value in estimating the capability of the lungs to diffuse oxygen and carbon dioxide. They frequently found the roentgenogram misleading, especially so when it revealed an extensive bilateral infiltration of the lungs, and in such instances, the ventilatory function was also markedly reduced. Yet, in spite of both reduction in ventilatory function and radiographic evidence of extensive involvement of the lungs, the diffusion test as measured by the rebreathing bag after standard



Figs. 2–7

exercise indicated that the lungs were capable of diffusing oxygen and carbon dioxide as well as the lungs in normal subjects.

The above may happen in acute pulmonary disease where a good deal of both lungs is involved and the ventilatory function is correspondingly reduced. The uninvolved lung tissue is still normal and the permeability to gases will be no different than that in normal lungs. However, should the diseased areas in the lungs persist for a long period of time, the uninvolved lung tissue may gradually become emphysematous and changes in permeability take place.

Apparently the ventilation occurs only in the uninvolved areas of the lungs, otherwise the diffusion of oxygen and carbon dioxide could not be in the normal range. The authors believe that impaired lung tissues take little or no part in the ventilatory phase of pulmonary function. The inspired air by-passes the impaired lung areas.

The entering of air into one or the other lung depends on two factors: first, the tensile strength of one lung compared to the other and, second, to conditions reducing the lumen of the bronchi leading to a lung, lobe, lobule etc. In normal lungs, air enters equally into both lungs. In disease, one lung may develop

---

FIG. 2. (Upper left) A roentgenogram of the lungs of a white male of 39 years with a bilateral silicosis, whose ventilatory capacity was reduced considerably (A.V.C. 1,700 cc. and C.N.V.C. 3,700 cc.). The patient was dyspneic on the least exertion. The diffusion test revealed a decrease in oxygen diffusion (oxygen 11.8 volume per cent; carbon dioxide 6.92 volume per cent). This patient had both ventilatory and permeability dysfunction.

FIG. 3. (Upper right) A roentgenogram of the lungs of a white female of 38 years with an endobronchial tuberculosis in the left main bronchus and a tuberculous infiltration in the left upper lobe. She had good ventilatory capacity (A.V.C. 2,400 cc.; C.N.V.C. 3,400 cc.). Her test for diffusion of oxygen was very good and below the mean normal of 8.3 volume per cent for females (oxygen 7.77 volume per cent; carbon dioxide 8.03 volume per cent). Because of the shift of the mediastinum to the left we may assume the whole ventilatory and diffusion processes probably occur in the right lung. (See figure 4.)

FIG. 4. (Centre left) A roentgenogram of a case of left endobronchial tuberculosis taken in expiration revealing the shift of the mediastinum to the right. For details see figure 3.

FIG. 5. (Centre right) A roentgenogram of the lungs of a patient with a far advanced bilateral pulmonary tuberculosis. The patient, in spite of an advanced bilateral tuberculosis, had fairly good ventilatory capacity and evidence that the uninvolved lung tissues were capable of diffusing oxygen. The A.V.C. was 3,400 cc. compared to a C.N.V.C. of 4,400 cc. The diffusion test to oxygen and carbon dioxide was oxygen 8.7 volume per cent and carbon dioxide 7.9 volume per cent. Surprisingly, there was both good ventilatory and diffusion function for an advanced tuberculous disease.

FIG. 6. (Lower left) A roentgenogram of a 65 year old white male with a minimal pulmonary tuberculosis involving chiefly the right lung. The ventilatory capacity was good (A.V.C. 3,500 cc. and C.N.V.C. 4,600 cc.). The ability of the lung to oxygen diffusion, on the other hand, was poor (oxygen 11.4 volume per cent; carbon dioxide 6.7 volume per cent).

FIG. 7. (Lower right) A roentgenogram of a white male of 34 years with a bilateral pulmonary tuberculosis, involving chiefly the right lung. The ventilatory capacity was reduced to about the threshold between dyspnea and normal comfort on exertion (about 63 per cent of the C.N.V.C.). The uninvolved areas of the lungs appear to be emphysematous in the roentgenogram. The diffusion test for oxygen was good which definitely ruled out the diagnosis of emphysema (oxygen 8.43 volume per cent; carbon dioxide 8.01 volume per cent).

more tensile strength than the other. The lung with the lesser tensile strength expands while little air enters into the one with the greater tensile strength. We formed such impressions in our study of 170 cases of impaired lungs. We decided that in patients with marked impairment of ventilatory function the gases in the rebreathing bag were in equilibrium only with the pulmonary arterial circulation in the lung tissues capable of being ventilated. The rebreathing bag test only measured the diffusion of oxygen and carbon dioxide in the lung tissues the air in the bag could reach.

With the above impressions in mind, we decided to reproduce similar situations in a negative pressure jar with the use of a Y-tube to represent the trachea and the division into two main bronchi. We closed a jar with a rubber stopper having three openings. Through one we inserted the stem of the Y-tube so that both arms were in the jar. Through the second opening a glass tube was inserted connecting the inside of the jar to a negative pressure pump. Through the third opening a glass tube was inserted, connecting the inside of the jar to a water manometer. The stem of the Y-tube was open to the atmospheric air. Two balloons representing the lungs were attached to the arms of the Y-tube enclosed in the jar. There was a 1.9 cm. water difference in the tensile strength of the two balloons. When a sufficient negative pressure was induced in the jar, the balloon of lesser tensile strength began to expand and continued to enlarge as the negative pressure increased until it finally burst with negligible expansion of the balloon of greater tensile strength. The above phenomenon also occurs in lung tissue. Impairment of lung tissue because of disease decreases the elasticity of the lung and increases its tensile strength. Changes in the pleura in a similar manner increase the tensile strength of the lung.

In partial obstruction of a bronchus, the current of air moves to the unobstructed one and the involved bronchus is practically by-passed by the moving columns of air. This phenomenon can be observed by placing both limbs of a Y-tube in a beaker of water and blowing through the stem of the Y-tube. The arms of the tubes should be about 1 cm. below the surface of the water; very little blowing force is required for the demonstration. The lumen of one of the arms of the Y-tube is then reduced in width. The bubbles of air will be seen emerging from the unobstructed arm of the Y-tube with an occasional bubble coming through the arm with the reduced lumen.

In the tracheobronchial tree the columns of air similarily move to the unobstructed bronchus. This phenomenon is seen in partial obstruction of one of the major bronchi (carcinoma, tuberculous endobronchitis, etc.). In partial obstruction of one of the main bronchi, the lung supplied by the unobstructed bronchus expands and forces the mediastinum (if mobile) towards the opposite lung. The unobstructed lung on expiration, having no difficulty in expelling its gases, retracts to a small area compared to the partially obstructed lung which now appears in the roentgenogram (figure 3 and 4) equal or larger than the normal contralateral lung. The mediastinum now has shifted towards the normal lung.

We then experimented with one partially obstructed arm of a Y-tube and two balloons of unequal tensile strength. We were surprised to find that the balloon with the lesser tensile strength would expand even when the lumen of the arm of the Y-tube was partly obstructed. From the above we assumed the most important factor in ventilation of lung tissue is the tensile strength of the lung and is even a greater factor than changes in the lumen of the bronchi.

The above phenomena occur in diseased lungs. Either due to disease in the lung or pleura the tensile strength is increased and the ability of the diseased areas of lungs to ventilate is lost. The rebreathing bag test after the standard exercise is only a measurement of the diffusion of oxygen and carbon dioxide of the lung tissues able to ventilate.

How the pulmonary arterial circulation is affected in the unventilated lung tissues needs a good deal of clarification. Some investigators believe the blood circulating through unventilated lung tissues is returned to the left heart through the pulmonary veins as venous blood and thus pollutes the general circulation with venous blood in a similar manner, as in congenital heart disease. Other investigators think that the pulmonary arterial circulation is almost absent in the unventilated lung—as in pneumothorax, in collapse therapy, etc. The rebreathing test is not a measure of the diffusion of oxygen and carbon dioxide in the unventilated lung but only in the lung tissues capable of ventilation.

An impaired lung that has not functioned because of an increased tensile strength may again ventilate if the contralateral lung at some future time develops a still greater tensile strength than the previously impaired nonfunctioning lung. An example of the above is the reëxpanded lung after artificial pneumothorax which has increased considerably its tensile strength compared to the functioning contralateral lung. Should the contralateral lung become diseased and its tensile strength become equal to or greater than the reëxpanded lung, the latter will now participate in the ventilatory and diffusion functions.

The authors found by means of the rebreathing test after the standard exercise that the capability of the lung tissue able to function could be determined and the departure from the normal could be stated by comparing the results of the analysis of the oxygen and carbon dioxide in the rebreathing bag with the mean average as found in normal males and females.

The following cases illustrate the above. The first two examples are patients with good ventilatory tests but differ in the ability to diffuse oxygen and carbon dioxide.

Case H. H.: The patient is a male, 21 years of age. He had a far advanced bilateral caseous pneumonic pulmonary tuberculosis. The tuberculous disease involved chiefly the left lung (figure 5). The A.V.C. was 3,400 cc. and the C.N.V.C. was 4,400 cc. The A.V.C. was 77 per cent of the C.N.V.C. Thus we have a patient with considerable pulmonary disease and yet sufficient ventilatory function. (As explained previously, 60 per cent of the C.N.V.C. is the threshold between comfort and dyspnea, with no symptoms of dyspnea on walking on level ground.)

A rebreathing test after the standard exercise was done. The oxygen was 8.7 volume

per cent and the carbon dioxide was 7.9 volume per cent. The ability of the lung tissues functioning to diffuse oxygen and carbon dioxide was normal compared to the control normal male subjects.

Case J. R.: A white male of 65 years had a minimal pulmonary tuberculosis involving the right upper lobe (figure 6). The character of the tuberculous disease was caseous pneumonic. There was an atelectasis of the posterior segment of the right upper lobe and in the atelectatic area, a small cavity. Small areas of bronchogenic disseminated tuberculosis were scattered through the midportion of the right lung.

The A.V.C. was 3,500 cc. and the C.N.V.C. was 4,600 cc. The actual vital capacity was 76 per cent of the C.N.V.C. The above vital capacity is about the same as in case H. H. above. A rebreathing test after the standard exercise was done. The oxygen was 11.42 volume per cent and the carbon dioxide was 6.78 volume per cent. Compared to the mean normal male volume percentages of oxygen and carbon dioxide there is considerable impairment of the lung tissue to diffuse oxygen and carbon dioxide.

In comparing these 2 cases with each other we find one patient with extensive disease of the lungs with a fair ventilatory capacity and good diffusion of oxygen and carbon dioxide in the lung tissues in contrast to a patient with much less pulmonary disease, as noted in the roentgenogram in figure 5, with equally good ventilatory capacity but poor diffusion of oxygen and carbon dioxide.

The difference in the diffusion rate in the two lung tissues can be noted more graphically by converting the volume percentages of the oxygen and carbon dioxide to their pressure in mercury. The first case, H. H., had a 8.7 per cent volume of oxygen or 62.03 mm. of Hg. (good diffusion) compared to case J. R. in which the oxygen volume was 11.92 per cent and the oxygen pressure 81.42 mm. of Hg. (poor diffusion). The carbon dioxide pressure in the first case was 56.32 mm. of Hg. whereas in the second case the pressure was 48.28 mm. of Hg.

The next reported cases are a ventilatory group with about 60 per cent of the C.N.V.C. (Threshold between comfort and dyspnea.)

Case G. M.: is a white male, 34 years of age. He had a bilateral pulmonary tuberculosis, moderately advanced, caseous pneumonic in character, which involved chiefly the right lung (figure 7). The tuberculosis was in a chronic stage with evidence of fibrosis and calcification. In the right upper lobe there was a small cavity. Both lungs suggested a diffuse fibrosis with a complicating emphysema. Both diaphragms appeared as though they were fixed. The roentgenogram suggested the uninvolved lung tissues to be emphysematous with poor diffusion of oxygen and carbon dioxide. The A.V.C. was 63 per cent of the C.N.V.C.

A rebreathing test after the standard exercise revealed that the lung functioning was normally permeable to oxygen and carbon dioxide. The oxygen was 8.43 volume per cent and the carbon dioxide was 8.01 volume per cent, a very excellent diffusion of oxygen and carbon dioxide. This case is a good example how difficult it is to judge ability of the lungs to diffuse gases from diminished ventilatory capacity and roentgenograms of impaired lungs. There certainly was no emphysema of the lungs which the roentgenogram suggested.

Case W. S. was a white male, 65 years of age. The pulmonary tuberculosis in the right lung was minimal. A small fibrotic tuberculous lesion was in the mediastinal aspect of the right upper lobe (figure 8). The roentgenograms of the lungs revealed much less tuberculosis and suggested better ability to diffuse gases than did the roentgenograms of the lungs in the preceding case. The A.V.C. was 2,600 cc. and the C.N.V.C. was 4,200 cc. The A.V.C. was 62 per cent of the C.N.V.C.

A rebreathing test after the standard exercise was done. The oxygen was 11 volume per cent and the carbon dioxide was 7.38 volume per cent. The ability of the functioning lung tissues to diffuse oxygen showed marked impairment while the roentgenogram suggested better ability to diffuse oxygen than the roentgenogram did in the case of G.M. Both patients had diminished ventilatory capacities.

Case R. P. was a white male, 63 years of age. He had a moderately advanced pulmonary tuberculosis involving the left upper lobe. The roentgenogram of the lungs (figure 9) suggested an emphysema complicating pulmonary tuberculosis. The A.V.C. was 2,200 cc. and the C.N.V.C. was 4,700 cc. The A.V.C. was 47 per cent of the C.N.V.C.

A rebreathing test after the standard exercise was done. The oxygen was 8.27 volume per cent and the carbon dioxide was 7.9 volume per cent. The diffusion ability of the functioning lung tissue was normal. We include this case because of the patient's age of 63 years to dispel any thought that age may be a factor in poor diffusion. Though the ventilatory capacity was reduced to below 50 per cent of the C.N.V.C. and the roentgenogram suggested a severe emphysema of the lungs and the patient's age was 63 years, the functioning lung tissues showed a normal capability to diffuse oxygen and carbon dioxide.

Even with the ventilatory capacity reduced to below 40 per cent of the C.N.V.C. we find that the lung tissues capable of ventilating could still diffuse oxygen and carbon dioxide normally.

Case B. J. was a male Negro, 18 years of age with a far advanced caseous pneumonic pulmonary tuberculosis. The roentgenogram of the lungs (figure 10) revealed the right lung collapsed by an artificial pneumothorax. The upper lobe was well collapsed, atelectatic and contained a ball-valve cavity that was still patent. There was a long thick pleural adhesion suspending the upper lobe from the posterior axillary area of the thoracic cavity. The middle lobe and lower lobe were about 40 per cent collapsed. There was a diffuse bronchogenic spread through the whole left lung.

The A.V.C. was 1,800 cc. and the C.N.V.C. was 4,900 cc. The A.V.C. was only 37 per cent of the C.N.V.C. The collapse of the right lung and the disseminated tuberculous disease in the left lung suggested poor diffusion of gases in the remaining functioning lung.

A rebreathing test after the standard exercise was done. The oxygen was 7.52 volume per cent and the carbon dioxide was 7.52 volume per cent. The ability to diffuse oxygen and carbon dioxide was even better than the mean oxygen volume percentage in the average normal male lung (7.9 volume per cent).

On the other hand, *case H. M.* (figure 11), a Chinese male of 39 years, with an A.V.C. 39 per cent of the C.N.V.C. (A.V.C. 1,500 cc.; C.N.V.C. 3,800 cc.) had a bilateral far advanced pulmonary tuberculosis with cavity formation in both upper lobes. The roentgenogram of the lungs revealed there was less tuberculosis in the lungs than in the previous case, B. J.

Figs. 8–13

The rebreathing test after the standard exercise was done. The oxygen was 11.66 volume per cent and the carbon dioxide was 6.88 volume per cent. The ability to diffuse oxygen of the lung tissue functioning was much impaired in contrast to the above case. As a rule when the ventilatory capacity is reduced to below 40 per cent of the C.N.V.C. the ability of the functioning lung tissue to diffuse oxygen and carbon dioxide is impaired.

We found the rebreathing bag test after the standard exercise valuable in determining the ability of the contralateral lung to diffuse gases in pneumothorax therapy, especially so when the A.V.C. was reduced to below 50 per cent of the C.N.V.C. (Figures 12, 13 and 14 are roentgenograms of the lungs of such patients.)

Case N. Y. (figure 12) was a male of 28 years. His A.V.C. was 2,100 cc. and his C.N.V.C. was 4,600 cc. The A.V.C. was 45 per cent of the C.N.V.C. A rebreathing bag test after the standard exercise was done. The oxygen was 8.36 volume per cent and the carbon dioxide was 8.86 volume per cent. The diffusion of oxygen and carbon dioxide was within the normal range.

Case R. R. (figure 13) was a male of 28 years. His A.V.C. was 2,000 cc. and his C.N.V.C. was 4,500 cc. The A.V.C. was 44 per cent of the C.N.V.C. A rebreathing bag test after the standard exercise was done. The oxygen was 8.32 volume per cent and the

---

Fig. 8. (Upper left) A roentgenogram of a white male of 65 years of age. This roentgenogram revealed much less impairment of lung tissue than the roentgenogram in figure 7. The uninvolved lung tissues suggested much better diffusion of oxygen than in the roentgenogram of figure 7. However, the ability to diffuse oxygen was poor (oxygen 11 volume per cent; carbon dioxide 7.38 volume per cent).

Fig. 9. (Upper right) A roentgenogram of the lungs of a white male, 65 years of age, which suggests an emphysema of both lungs complicating a moderately advanced pulmonary tuberculosis in the left upper lobe. The ventilatory capacity was considerably reduced (47 per cent of the C.N.V.C.). The diffusion test for oxygen however was good (oxygen 8.27 volume per cent; carbon dioxide 7.9 volume per cent).

Fig. 10. (Centre left) A roentgenogram of the lungs of a young Negro male. The ventilatory capacity was greatly reduced (37 per cent of the C.N.V.C.). Though the roentgenogram suggested poor capability to diffuse oxygen, the test revealed very excellent diffusion of oxygen (oxygen 7.52 volume per cent; carbon dioxide 7.52 volume per cent).

Fig. 11. (Centre right) This roentgenogram, in contrast to the roentgenogram in figure 10, reveals much less involvement of the lungs. The ventilatory capacity was reduced in this patient to the same extent as in the patient shown in figure 10. The test for the diffusion of oxygen however was very poor (oxygen 11.66 volume per cent; carbon dioxide 6.88 volume per cent). This patient had both very poor ventilatory and diffusion function tests.

Fig. 12. (Lower left) A roentgenogram of the lungs of a patient with a left artificial pneumothorax. The ventilatory capacity was reduced to 46 per cent of the C.N.V.C. A test for the diffusion of oxygen revealed good diffusion to oxygen (oxygen 8.36 volume per cent; carbon dioxide 8.86 volume per cent).

Fig. 13. (Lower right) A roentgenogram of the lungs of a patient with a right artificial pneumothorax and a spread of the tuberculous disease into the upper half of the left lung. The ventilatory function was much reduced (44 per cent of the calculated normal). The question was whether the left lung could be treated surgically. The diffusion test revealed that the functioning areas of lung could diffuse oxygen well (oxygen 8.32 volume per cent; carbon dioxide 7.67 volume per cent).

carbon dioxide was 7.67 volume per cent. The ability of the contralateral functioning lung to diffuse gases was within the normal range.

In *case J. W.* (figure 14), in whom the A.V.C. was 47 per cent of the C.N.V.C., the functioning left lung showed poor diffusion of oxygen as the rebreathing bag test after the standard exercise revealed. The oxygen was 10.79 volume per cent and the carbon dioxide was 7.53 volume per cent.

The diffusion test is also of value in selecting cases for pneumonectomy. The diffusion of oxygen in the nondiseased lung may be determined, as in the following cases.

Case M. H. (figure 15) was a female of 18 years. Her A.V.C. was 1,300 cc. and her C.N.V.C. was 2,700 cc. The A.V.C. was 48 per cent of the C.N.V.C. Her roentgenogram revealed an atelectasis of the left lung due to a far advanced caseous pneumonic tuberculosis.

A rebreathing bag test after the standard exercise was done. The oxygen volume per cent was 8.89 and carbon dioxide volume per cent was 7.51. The right lung showed normal diffusion of oxygen and carbon dioxide.

Case W. P. (figure 16), a white male of 20 years, had an atelectasis of the left lung due to a caseous pneumonic tuberculosis. The right lung was also involved. The upper lobe had a tuberculous infiltration which was fibrotic in character. There was no evidence of cavitary formation in the right lung. The A.V.C. was 2,300 cc. and the C.N.V.C. was 4,600 cc. The A.V.C. was 50 per cent of the C.N.V.C.

A rebreathing bag test was done after the standard exercise. The oxygen was 8.94 volume per cent and the carbon dioxide was 8.32 volume per cent. The right lung which was functioning revealed good diffusion of oxygen and carbon dioxide.

DISCUSSION

The diffusion of oxygen and carbon dioxide through the alveoli of the lungs may be measured by a rebreathing bag test after a standard exercise. The method, the norms and the diffusion in impaired lungs have been described in the text.

The authors are presenting some of the discussions that have been brought to their attention in regard to this test being a measure of the permeability of the alveolar tissues or a combination of many other factors. The following factors were brought up for discussion: (*1*) the potentially unequal or ineffectual emptying of the lungs; (*2*) the oxygen in the rebreathing bag may be high if the alveolar oxygen is high to begin with; (*3*) the same results would be obtained in the presence of a large residual air; (*4*) if the cardiac output, that is, the oxygen transport is reduced; (*5*) if the metabolic rate of the patient is subnormal; (*6*) the question of the recirculation of blood affecting the test; and (*7*) if the membrane between the alveoli and the capillaries is less permeable than normal.

(*1*) The potentially unequal or ineffectual emptying of the lung was discussed as a factor The authors have previously pointed out that, in the investigation of 8 normal young males in whom the thorax and abdomen was encircled in a canvas jacket in a manner that restricted the movements of the thorax and the diaphragms and resulted in a reduction of the vital capacities to

Figs. 14–16

Fig. 14. (Upper) A roentgenogram of the lungs of a patient with a right artificial pneumothorax. In contrast to the roentgenograms in figures 12 and 13, the diffusion of oxygen was poor as well as the ventilatory function. Ventilatory capacity was 57 per cent of the C.N.V.C. and the diffusion test was: oxygen 10.79 volume per cent; carbon dioxide 7.53 volume per cent.

Fig. 15. (Lower left) A roentgenogram of the lungs of a white female of 18 years. She had an atelectasis of the left lung, which was involved from apex to base. The question arose as to whether her right lung was able to function properly because a pneumonectomy was considered. Her ventilatory capacity was much reduced (48 per cent of the C.N.V.C.). A test for the diffusion of oxygen revealed good function (oxygen 8.89 volume per cent; carbon dioxide 7.51 volume per cent).

Fig. 16. (Lower right) A roentgenogram of the lungs of a white male, 20 years of age. The ability of the right lung to diffuse oxygen was considered for possibility of a pneumonectomy of the left lung. The ventilatory capacity was found to be reduced to 50 per cent of the C.N.V.C. The test for the diffusion of oxygen revealed good diffusion of oxygen (oxygen 8.94 volume per cent; carbon dioxide 8.32 volume per cent).

below 50 per cent or more of their calculated normal vital capacities, there was very little change in the oxygen and carbon dioxide diffusion before and after applying the canvas jacket. (See text and table 3 for details.)

(2) The next factor that came up for discussion was whether the oxygen in the rebreathing bag may be affected by the volume percentage of the oxygen and

TABLE 5

Thirty cases showing relationship of alveolar oxygen and carbon dioxide at rest to the oxygen and carbon dioxide in the rebreathing bag after exercise*

CASES	VOLUME PERCENTAGES IN REBREATHING BAG AFTER STANDARD EXERCISE		ALVEOLAR AIR AT REST*	
	O_2	CO_2	O_2	CO_2
1. H. H.	8.74%	7.58%	13.20%	5.81%
2. S. S.	9.81%	7.61%	13.81%	5.32%
3. K. G.	8.67%	8.20%	13.33%	5.41%
4. W. T.	10.47%	7.39%	12.67%	5.74%
5. A. J.	9.60%	7.43%	14.53%	4.90%
6. M. R.	11.30%	7.06%	12.60%	5.56%
7. L. R.	7.83%	8.72%	14.20%	5.06%
8. M. D.	7.77%	8.03%	13.70%	5.45%
9. W. W.	9.13%	7.12%	13.16%	5.57%
10. J. B.	8.92%	8.01%	14.72%	4.48%
11. E. G.	11.89%	6.53%	13.21%	5.23%
12. E. T.	10.04%	7.65%	14.58%	4.47%
13. L. C.	6.20%	9.18%	14.15%	5.48%
14. N. T.	7.54%	7.74%	14.70%	4.92%
15. W. C.	9.20%	7.56%	12.56%	5.34%
16. W. V.	7.88%	7.77%	14.01%	4.83%
17. F. L.	8.21%	7.29%	12.90%	5.05%
18. W. B.	8.32%	7.71%	11.88%	5.97%
19. S. K.	8.28%	8.70%	13.89%	5.20%
20. J. C.	9.18%	6.98%	10.86%	5.67%
21. A. B.	11.69%	6.50%	13.16%	5.32%
22. W. B.	13.35%	5.72%	14.53%	4.68%
23. A. McC.	12.11%	6.61%	14.59%	5.08%
24. F. F.	8.68%	8.03%	13.75%	5.36%
25. I. P.	7.04%	7.01%	12.03%	5.32%
26. N. T.	8.10%	8.78%	13.58%	5.31%
27. T. H.	13.07%	6.38%	11.25%	6.32%
28. H. S.	12.92%	6.69%	12.14%	6.66%
29. G. M.	11.64%	6.28%	11.41%	5.93%

* Rest—Subject sits quietly in a chair for thirty minutes.

carbon dioxide in the alveolar air. Would the volume per cent of oxygen in the rebreathing bag be high if the alveolar oxygen is high to begin with?

A glance through table 5 reveals that there is no relationship between the volume per cent of oxygen and carbon dioxide in the rebreathing bag after the standard exercise and the volume per cent of oxygen and carbon dioxide in the alveolar air at rest. Best and Taylor (14) give the following figures for alveolar

oxygen and carbon dioxide, reduced to standard temperature and pressure: oxygen 14.29 per cent and carbon dioxide 5.5 per cent. The reader will find in table 5 evidence that subjects with such alveolar percentage of oxygen and carbon dioxide may have either high or low volume per cent of oxygen and carbon dioxide in the rebreathing bag after the standard exercise test. A perusal through table 5 shows that there is no relationship between the alveolar oxygen and carbon dioxide at rest and the results of the test measuring the diffusion of oxygen and carbon dioxide in the lungs.

(3) The next factor for discussion was that a large residual air would give a high oxygen per cent in the rebreathing bag. The authors found evidence of bad diffusion of oxygen and carbon dioxide in true cases of emphysema of the lungs. Unfortunately we did not measure the residual air in these cases. The authors also presented a case in which the ventilatory capacity was considerably reduced; the roentgenogram of case G.M. (figure 7) suggested emphysematous lungs but the diffusion test revealed good diffusion of oxygen and carbon dioxide. The wide intercostal spaces did suggest emphysema of the lung and a large volume of residual air. The diffusion test eliminated the diagnosis of emphysema of the lung.

(4) The next factor for discussion is the rôle which the cardiac output played in the test. The cardiac output was discussed hotly but the authors believe it plays no rôle, or a very minor one, and base their opinion on the following facts.

A: They were able to establish average mean normals in 23 males and 25 females and assumed there was a sufficient variance in the strength of the right ventricular contraction and in the flow of blood through the pulmonary circulation in these 48 normal subjects to have seriously affected the mean average volume per cent of oxygen and carbon dioxide if the right ventricle and pulmonary arterial circulation played any important rôle in the interchange of gases in the lung. The authors wish to stress the fact that there is a standard exercise associated with this test which should both affect the ventricular stroke and the pulmonary circulation.

B: The aspiratory action of the thorax and its effect on the superior and inferior venae cavae and the right auricle have been known a long time. We wish to quote Howell (13): "The negative pressure prevailing in the thoracic cavity must affect the organs in the mediastinal space. The main effect of the difference in pressure is felt upon the lymph and blood, especially the latter. The large veins in the neck and axilla are under pressure of an atmosphere exerted through the skin and the same is true for the inferior cava in the abdomen. But the superior and inferior cavae and the right auricle are under pressure of less than one atmosphere. This difference in the pressure must act as a constant favoring condition to the flow of blood to the heart. The difference is markedly increased in each inspiration so that at each such act there is an increase in the velocity and volume of flow in the heart—an effect which is usually referred to as the aspiratory action of the thorax. At each inspiration blood is 'sucked' from the extrathoracic into the intrathoracic veins. So far as the inferior cava is concerned, this effect is augumented by the simultaneous increase

in abdominal pressure. For as the diaphragm descends it raises the pressure of the abdomen as it lowers the pressure in the thorax. The two factors coöperate in forcing more blood from the abdominal to the thoracic portion of the cava. The changes in intrathoracic pressure during respiration must affect the blood flow also in the pulmonary circuit, the flow from the right to the left side of the heart."

The applying of a canvas jacket to the thorax and the abdomen, which would affect the movement of the thoracic cage and inhibit the movement of the diaphragms, would interfere with this aspiratory suction action and would reduce the vital capacity and affect the flow of blood to the right auricle and possibly affect the right ventricular volume and the blood flow in the pulmonary circuit. Such an experiment on 8 normal males was reported in the text and revealed no more than very unimportant minimal changes in the diffusion of oxygen and carbon dioxide before and after the thorax and abdomen were strapped in a canvas jacket (table 3). The A.V.C. was reduced to below 50 per cent of the C.N.V.C. in all the 8 normal males and dyspnea on exertion was present in all. Apparently the reduction of the aspiratory action of the thorax, which affects both venae cavae, the right auricle and indirectly the blood flow in the pulmonary circuit, had no influence on the diffusion of oxygen and carbon dioxide in normal males.

(5) The question of a low metabolic rate affecting the test was raised. The authors found no relationship in a small number of cases in which both tests were done.

(6) The time of the recirculation of the blood has also come up for discussion. As the authors have previously pointed out they used the rebreathing bag after the method of Plesch for the determination of venous carbon dioxide because Plesch assumed the recirculation time to be twenty seconds. Henderson and Prince, and Best and Taylor agreed with Plesch as to the twenty seconds for the recirculation of the blood. Other investigators have disagreed with the above figures and assumed that the time element is much shorter. The authors believe that in exercise the recirculation time must be less than twenty seconds. In our first experiment with the rebreathing bag we used thirty-five seconds for abnormal cases. We found, however, that the normal subjects could not go beyond twenty seconds and would pull their masks off their faces. Apparently subjects with very poor diffusion tolerate the test best. Their carbon dioxide does not reach the high volume per cent of the normal subject and the oxygen in the rebreathing bag is not reduced to the extent of the normal subject. The subjects with impaired lungs seemed to go through the test with much more comfort than did the subjects with normal lungs. Even should there be a return of some venous blood it apparently has little effect on the results, because our comparison of the abnormal is made against the control findings. The same factors occur in the control and in the abnormal cases.

(7) The authors believe that the chief factor in this test is the permeability of the membrane between the alveoli and the capillaries to the diffusion of oxygen and carbon dioxide. They admit there is no definite proof that permeability

is the only factor, but from their experience believe that the other factors, if they exist, play a very minor rôle. In view of the above they are hesitant to call the test a permeability test and have referred to the test as a measure of the diffusion of oxygen and carbon dioxide in the lungs.

Having tried to answer all the questions that were presented, the authors are sure that many other questions will arise which could only be answered by further research. The authors wish to add another interesting phase in this experiment, namely the finding of a marked reduction in ventilatory capacity in the presence of good diffusion of oxygen and carbon dioxide, as measured by the rebreathing bag test.

At first the above seemed incongruous. We had cases in which both lungs were involved and where we expected to obtain evidence of poor diffusion only to find the diffusion of oxygen and carbon dioxide within the normal range or better. We believe that only the uninvolved lung tissues are ventilated and the diseased areas are not. In the rebreathing bag test the gases in the rebreathing bag are only in equilibrium with the lung tissues capable of ventilation. In the text we have discussed the importance of the tensile strength of lung tissue with ventilation. We discussed the by-passing of lung tissue of increased tensile strength and how the columns of air only reach the lung areas of lesser tensile strength. The rebreathing bag test is a measurement of the diffusion of oxygen and carbon dioxide in the lung tissues capable of ventilation.

SUMMARY

1. The ventilatory and diffusion phases of pulmonary function are discussed.
2. Methods of ventilatory measurements are discussed.
3. The authors stress that the most valuable ventilatory measurement is a ventilatory reserve based on the number of times the maximum minute breathing capacity is greater than the resting minute ventilation. The normal in males is twenty times the resting minute ventilation. The normal in females is thirteen times the resting minute ventilation.
4. A method for measuring the diffusion of oxygen and carbon dioxide in the lungs is described.
5. The ability of lung tissues to diffuse oxygen and carbon dioxide, as measured by a rebreathing bag test after a standard exercise, was recorded in 23 normal males and 25 normal females.
6. Case reports of impaired lungs with their diffusion tests to oxygen and carbon dioxide are presented. The impressions of the authors have been based on such tests on 170 patients with impaired lungs.
7. A concept of ventilation of lung tissue, based on the tensile strength of normal and diseased lung tissues, is discussed

SUMARIO

1. Repásanse las fases de ventilación y difusión de la función pulmonar.
2. Discútense técnicas para mediciones de la ventilación.
3. Recálcase que la medición ventilatoria más valiosa consiste en determinar

el número de veces que la capacidad respiratoria máxima por minuto es mayor que la ventilación por minuto en reposo. Lo normal en los varones es una reserva ventilatoria 20 veces y en la mujer 13 veces mayor que la ventilación por minuto en reposo.

4. Descríbese una técnica para medir la difusión de oxígeno y bióxido de carbono en los pulmones.

5. En 23 varones normales y 25 mujeres normales se registró la capacidad de los tejidos pulmonares para difundir oxígeno y bióxido de carbono, medida por un ensayo en bolsa de la sobre-respiración (rebreathing) después de un ejercicio tipo.

6. Preséntanse pruebas de difusión del oxígeno y del bióxido de carbono en pulmones afectados con las correspondientes historias clínicas, basando los autores sus impresiones en el resultado de esas pruebas en 170 enfermos.

7. Preséntase un concepto de la ventilación del tejido pulmonar basado en la fuerza tensil de los tejidos pulmonares normales y patológicos.

REFERENCES

(1) Siebeck, R.: Die funktionelle Bedeutung der Atemmechanik und die Lungenventilation bei kardialer Dyspnoe, Deutsches Arch. f. klin. Med., 1912, *107*, 252.

(2) Peabody, Francis N., Wentworth, John A., and Barker, Bertha I.: The B. M. R. and the minute volume of the respiration of patients with cardiac disease, Arch. Int. Med., 1917, *20*, 468.

(3) Sturgis, Cyrus C., Peabody, Francis N., Hall, Francis C., and Fremont-Smith, Frank, Jr.: Relation of dyspnoea to the maximum minute ventilation, Arch. Int. Med., 1922, *29*, 235.

(4) Kaltreider, N. L., and McCann, N. S.: Respiratory response during exercise in pulmonary fibrosis and emphysema, J. Clin. Investigation, 1937, *16*, 23.

(5) Ornstein, George G., and Epstein, Israel G.: Spirometry as a procedure of determining pulmonary efficiency in pulmonary and heart disease: The failure of the X-ray of the chest in estimating pulmonary reserve, J. M. Soc. New Jersey, August, 1940.

(6) Hermannsen, J.: Untersuchungen über die maximale Ventilationsgrösse, (Atemgrenzwert), Ztschr. f. d. ges. exper. Med., 1933, *90*, 130.

(7) Cournand, A., Richards, D. W., Jr., and Darling, R. C.: Graphic tracings of respiration in pulmonary disease, Am. Rev. Tuberc., 1939, *40*, 487.

(8) Cournand, A., and Richards, D. W., Jr.: Pulmonary insufficiency, Amer. Rev. Tuberc., 1941, *44*, 26.

(9) Plesch, J.: Hämodynamische Studien, Ztschr. f. exper. Pathol. u. Therap., 1909, *6*, 380.

(10) Henderson, Y., and Prince, A.: Applications of gas analysis, J. Biol. Chem., 1917, *32*, 325.

(11) Best, C., and Taylor, N.: The physiological Basis of Medical Practice, W. Wood & Co., 1937.

(12) MacLeod, J. J. R.: Physiology in Modern Medicine, C. V. Mosby Co., St. Louis, 1935, p. 343.

(13) Howell, William Henry: Textbook of Physiology, W. B. Saunders & Co., 1901, p. 653.

(14) Best, C., and Taylor, N.: The Physiological Basis of Medical Practice. W. Wood & Co., 1939, p. 511.

SURGERY IN THE TUBERCULOUS PATIENT WITH AMYLOIDOSIS

OSCAR AUERBACH[1] AND MARGUERITE G. STEMMERMANN[2]

Whenever the tuberculous patient is confronted with the necessity of major surgery, the problem of amyloidosis arises. In approximately 10 per cent of cases in Sea View Hospital, an institution devoted to the care of the tuberculous, this complication is present either when surgery is contemplated or before the surgical stages have been completed. The decision, whether or not to operate, is a critical one. To those who favor the possibility of the resorption of amyloid, operation to control the etiological factor in the production of this substance appears essential. To the equally reliable observers who doubt that amyloid can be resorbed, the decision to operate must depend upon the extent of the amyloid depositions.

During the past ten years we have had the opportunity of studying 468 cases (22 per cent of our autopsy material) in whom amyloidosis was proved by post-mortem examination. Forty-three of these underwent 52 major surgical operations, following the detection of the amyloidosis (group A). On 43 additional patients, 77 operations were performed prior to the detection of amyloidosis (group B). Several of the patients in the first group had one or more surgical procedures a year or more before amyloidosis was demonstrable, but these operations are not included in this study (table 1).

It is our purpose to compare these two groups in order to determine whether or not major surgery should have been attempted; what complication, if any, directly attributable to amyloidosis may be expected postoperatively; and what can be done about these complications. To clarify the controversial question of resorption of amyloid, upon which the decision to operate at least partially depends, a review of this subject is indicated.

RESORPTION OF AMYLOID

The problem of resorption of amyloid has been attacked experimentally, first, by the implantation of amyloid tissue into healthy animals and, second, by the introduction of amyloid producing injections. In 1885, Litten (1) implanted portions of amyloid kidneys into the peritoneal cavities of guinea pigs and rabbits and in four to six months observed a typical foreign-body response. The kidney tissues were surrounded by vascular connective tissue and were firmly attached to the mesentery and omentum. Since the amyloid within the renal parenchyma gave a brown-red stain with iodine and ruby-red with methyl violet, rather than the conventional mahogany brown or rosy violet hue of amyloid, Litten concluded that the amyloid had been converted into hyaline. When Grigorjeff (2) repeated these experiments, he found a weakening of the specific staining qualities of the amyloid only where small amounts of the substance were

[1] Department of Pathology, Sea View Hospital, Staten Island, New York.
[2] Owen Clinic, Huntington, West Virginia.

TABLE 1

Group A

CASE	AGE	DISEASE	NUMBER OF OPERATIONS	OPERATION	CAUSE OF DEATH	EXTENT AMYLOID	POST-OPERATIVE DAY OF DEATH
1	50	Pul. T.B.	1	Thoracoplasty	Toxemia	Moderate	31
2	24	Pul. T.B.	1 (3*)	Thoracoplasty	Toxemia	Advanced	405
3	44	G.U. T.B.	1	Nephrectomy	Pul. T.B.	Moderate	292
4	37	Pul. T.B.	1	Thoracoplasty	Amyloid uremia	Advanced	90
5	22	Pul. T.B.	1	Thoracoplasty	Operative	Moderate	1
6	25	Pul. T.B.	1 (2)	Thoracoplasty	Pul. T.B.	Minimal	30
7	11	Bone T.B.	1	Bone fusion	Amyloid uremia	Advanced	1,296
8	15	Pul. T.B.	1	Laparotomy	Peritonitis	Minimal	6
9	38	Pul. T.B.	1	Laparotomy	Pul. T.B.	Moderate	85
10	16	Pul. T.B.	2	Thoracoplasty	Pul. T.B.	Advanced	10
11	32	Pul. Abscess	1	Lobectomy	Operative	Minimal	1
12	29	Pul. T.B.	2	Thoracoplasty	Pul. T.B.	Moderate	5
13	27	Bone T.B.	1	Bone fusion	Cardiac	Moderate	88
14	22	G.U. T.B.	1 (1)	Laparotomy	Pul. T.B.	Advanced	107
15	36	Pul. T.B.	1 (2)	Thoracoplasty	Pul. T.B.	Advanced	1,023
16	34	Pul. T.B.	1	Thoracoplasty	Pul. T.B.	Advanced	42
17	24	Pul. T.B.	1 (1)	Thoracoplasty	Pul. T.B.	Minimal	6
18	23	Pul. T.B.	1	Thoracoplasty	Cardiac	Moderate	28
19	15	Bone T.B.	1	Bone fusion	Amyloid uremia	Advanced	75
20	35	Pul. T.B.	1 (3)	Thoracoplasty	Amyloid uremia	Advanced	62
21	31	Pul. T.B.	2 (4)	Thoracoplasty	Pul. T.B.	Advanced	200
22	39	Pul. T.B.	1 (3)	Thoracoplasty	Pul. T.B.	Advanced	173
23	24	Bone T.B.	1	Bone Fusion	Meningitis	Advanced	215
24	38	Pul. T.B.	1 (1)	Thoracoplasty	Pul. T.B.	Moderate	32
25	26	Pul. T.B.	1 (2)	Thoracoplasty	Pul. T.B.	Advanced	841
26	24	Bone T.B.	1	Bone fusion	Meningitis	Moderate	77
27	40	Bronchiect.	1	Pneumonectomy	Operative	Minimal	11
28	33	Pul. T.B.	2	Thoracoplasty	Pul. T.B.	Moderate	15
29	38	Bone T.B.	1	Amputation	Pul. T.B.	Advanced	36
30	36	Bone T.B.	1	Bone fusion	Toxemia	Advanced	120
31	43	Pul. T.B.	1	Thoracoplasty	Pul. T.B.	Advanced	5
32	12	Pul. T.B.	2	Thoracoplasty	Pul. T.B.	Minimal	4
33	26	Pul. T.B.	1 (3)	Thoracoplasty	Pul. T.B.	Moderate	10
34	32	Pul. T.B.	2	Thoracoplasty	Pul. T.B.	Advanced	214
35	40	Pul. T.B.	1 (1)	Thoracoplasty	Pul. T.B.	Advanced	144
36	35	Pul. T.B.	2 (2)	Thoracoplasty	Amyloid uremia	Advanced	536
37	30	Pul. T.B.	1 (4)	Lobectomy	Amyloid uremia	Advanced	58
38	52	Syphilis	1	Prostatectomy	Amyloid uremia	Advanced	3
39	16	Bone T.B.	1	Bone fusion	Toxemia	Advanced	162
40	23	Pul. T.B.	1 (2)	Thoracoplasty	Toxemia	Advanced	285
41	26	Bone T.B.	1	Bone fusion	Operative	Minimal	1
42	13	Bone T.B.	1	Bone fusion	Amyloid uremia	Advanced	143
43	25	Pul. T.B.	3 (4)	Thoracoplasty	Transfusion	Moderate	6
Total			52 (39*)				

* Operations before development of amyloidosis and not included in this study.

TABLE 1a

Group B

CASE	AGE	DISEASE	NUMBER OF OPERATIONS	OPERATION	CAUSE OF DEATH	EXTENT AMYLOID	POSTOPERATIVE DAY OF DEATH
1	33	Bone T.B.	1	Bone fusion	Pul. T.B.	Minimal	69
2	54	Bone T.B.	2	Bone fusion	Peritonitis	Advanced	1,076
3	42	Bone T.B.	1	Bone fusion	Peritonitis	Advanced	1,420
4	33	Pul. T.B.	4	Thoracoplasty	Pul. T.B.	Moderate	1,330
5	53	Bone T.B.	3	Bone fusion	Toxemia	Advanced	392
6	33	G.U. T.B.	1	Nephrectomy	Pul. T.B.	Moderate	112
7	39	Pul. T.B.	5	Thoracoplasty	Toxemia	Moderate	652
8	38	Pul. T.B.	5	Thoracoplasty, pneumonectomy	Pul. T.B.	Advanced	367
9	16	Bone T.B.	1	Amputation	Toxemia	Advanced	506
10	28	Pul. T.B.	1	Pneumonectomy	Pul. T.B.	Minimal	76
11	38	Pul. T.B.	4	Thoracoplasty	Pul. T.B.	Minimal	244
12	42	G.U. T.B.	1	Nephrectomy	Amyloid uremia	Advanced	1,068
13	31	Pul. T.B.	2	Thoracoplasty	G.I. hemorrhage	Moderate	327
14	27	Bone T.B.	1	Bone fusion	Toxemia	Advanced	416
15	32	Bone T.B.	1	Amputation	Toxemia	Advanced	169
16	13	Bone T.B.	1	Bone fusion	Amyloid uremia	Advanced	1,604
17	11	Bone T.B.	1	Bone fusion	Toxemia	Advanced	1,102
18	43	Bone T.B.	1	Bone fusion	Pul. T.B.	Advanced	183
19	26	Bone T.B.	1	Bone fusion	Toxemia	Advanced	329
20	24	Bone T.B.	3	Bone fusion	Amyloid uremia	Advanced	17 yr.
21	31	Pul. T.B.	3	Thoracoplasty	Amyloid uremia	Advanced	1,068
22	33	Pul. T.B.	2	Thoracoplasty	Pul. T.B.	Moderate	714
23	52	Bone T.B.	1	Bone fusion	Amyloid uremia	Advanced	784
24	31	G.U. T.B.	1	Nephrectomy	Meningitis	Moderate	247
25	36	Bone T.B.	1	Bone fusion	Toxemia	Advanced	743
26	38	Bone T.B.	1	Bone fusion	Amyloid uremia	Advanced	5 yr.
27	33	G.U. T.B.	1	Nephrectomy	T.B. uremia	Advanced	4 yr.
28	8	Bone T.B.	1	Bone fusion	Bronchopneumonia	Advanced	5 yr.
29	36	Pul. T.B.	2	Thoracoplasty	Amyloid uremia	Advanced	268
30	39	Pul. T.B.	2	Thoracoplasty	Pul. T.B.	Advanced	844
31	29	Pul. T.B.	2	Thoracoplasty	Pul. T.B.	Advanced	265
32	40	Bone T.B.	1	Bone fusion	Amyloid uremia	Advanced	5 yr.
33	53	Pul. T.B.	2	Prostatectomy	Cardiac	Minimal	383
34	44	Bone T.B.	1	Amputation	Amyloid uremia	Advanced	672
35	25	Pul. T.B.	3	Thoracoplasty	Pul. T.B.	Advanced	397
36	28	Pul. T.B.	3	Thoracoplasty	Pul. T.B.	Minimal	667
37	26	Pul. T.B.	1	Laparotomy	Pul. T.B.	Advanced	612
38	33	Pul. T.B.	1	Thoracoplasty	Toxemia	Advanced	254
39	57	Pul. T.B.	1	Laparotomy	Carcinoma	Minimal	506
40	37	Pul. T.B.	2	Thoracoplasty	Peritonitis	Moderate	115
41	31	Pul. T.B.	3	Thoracoplasty	Pul. T.B.	Moderate	347
42	48	Pul. T.B.	1	Laparotomy	Pul. T.B.	Advanced	158
43	43	Pul. T.B.	1	Thoracoplasty	Pul. T.B.	Moderate	203
Total..................			77				

present. Larger amounts persistently retained their physical and chemical characteristics.

Since such results may be entirely attributable to the foreign-body response of the host, Dantchakow (3), utilizing pure *Staphylococcus aureus* cultures, interrupted the production of amyloidosis in rabbits, after he had established its presence by biopsy of the submaxillary gland. Although the results were not the same in all animals, there was evidence of resorption of the amyloid in the opposite gland two months after the cessation of the injections. The length of time necessary for resorption depended upon the amount of amyloid present. Where its extent was marked no resorption apparently had occurred, although the specific staining qualities of the amyloid were weaker.

Utilizing nutrose injections, which produce a more uniform and regular deposition of amyloid, Morgenstern (4) demonstrated resorption and complete disappearance of the substance within four months of cessation of the injections. To follow the course of resorption, he performed liver biopsies and noted groups of giant cells forming granulomata surrounding the amyloid and dividing it into parts. From similar experiments, Kuczynski (5) also demonstrated resorption, describing it as a dissolution phenomenon in the spleen and as an ingestive one in the liver.

Considering the relative ease with which resorption has been demonstrated experimentally, it is surprising that so few cases have been reported in man. Rosenblatt (6), Reimann (7), Walker (8), Grayzel *et al.* (9), Pearlman (10), Metraux (11), Waldenström (12) and others have cited cases, but many of these are open to question. Before the advent of the congo red test, the diagnosis of amyloidosis, except by biopsy, was most uncertain. Even the congo red test is not an infallible guide, as we have previously shown in a series of 649 tests, in which there were 4.2 per cent false positive reports (13).

Hepatomegaly and splenomegaly apparently may be misleading. In our 468 patients with amyloidosis, we found in some cases marked discrepancies between the extent of the amyloid and the size of these organs. In 113 of the group, huge livers were noted during life and at autopsy. Yet, in 17 of these, the enlargement was due rather to fatty infiltration than to amyloid and no relationship existed between the degree of amyloidosis and the extent of fatty degeneration. The size of the spleen is an even poorer guide to amyloidosis, since the commonest amyloidotic spleen is of the "sago" type which is normal or even small in size.

Edema, probably on a nutritional basis, is so commonly found in the critically ill tuberculous patient that it is of little diagnostic significance. If associated with marked (not slight) evidence of renal damage plus other evidence of amyloidosis, it carries greater weight as a diagnostic factor. We have never seen a patient come to autopsy with marked albuminuria, diminished renal concentrating power and 90 per cent or more absorption of congo red who did not have amyloidosis. Yet we have seen occasional cases with various combinations of these findings without amyloidosis.

Waldenström's (12) liver biopsy demonstration of amyloidosis furnishes unequivocal proof of the presence for the condition and, by this technique, he has

demonstrated the progressive resorption of amyloid during life. It is unfortunate that no one has repeated his experiments in a large series, but liver biopsies in man are not without danger. The procedure, nevertheless, is certainly less hazardous in the large, bloodless amyloid liver than in the normal organ.

On the biopsy rests the unequivocal proof of the presence of amyloidosis and it should, therefore, be used more extensively for this purpose. Recently at Sea View Hospital, we have been staining every tissue procured by biopsy or excisional surgery with methyl violet, in addition to the routine hemotoxylin eosin stain. In view of the fact that at autopsy we have found amyloid in at least the blood vessels of every organ of the body, it is not surprising that this biopsy material has disclosed depositions of amyloid in the villi of the gall bladder, sinus tracts and the gingivae. The latter is a particularly useful tissue since it is rich in small blood vessels, the site of the earliest amyloid depositions, and a small portion is easily and frequently essential to remove at the time of tooth extractions or pyorrhea prophylaxis. Although amyloid is not as frequently demonstrable in the gingivae as in the liver, their accessability should make them a useful source of serial biopsies to study resorption.

In our autopsy and biopsy experience we have never found evidence of the regression of amyloidosis, although admittedly we have never had the opportunity of studying at autopsy any case reputed to have had resorption of amyloid during life. In 8 of 468 cases (1.7 per cent), in spite of the fact that the basic disease was healed or arrested, there was no evidence of resorption in any organ. In none did we observe a weakened staining reaction, giant cells, granulomata, ingestion or dissolution. In 5 cases, the amyloid not only did not regress after the basic disease had healed, but actually had progressed and the patients died in amyloid uremia.

Notwithstanding the pessimistic impression provided by the autopsy table, it is not necessarily a true one. Obviously the pathologist rarely observes the better results of the surgeon or internist in controlling the basic disease. Even if resorption of amyloid is infrequent, there is every reason to believe that in most cases control of the underlying infection will not only prevent the development of amyloidosis, but curtail its deposition at a level where it will least disturb the function of the involved viscera.

SURGICAL ASPECTS

In 7 patients, all in group A, although draining sinuses persisted, quiescence or arrest of the underlying infection was obtained by surgery. The remainder cannot all be assumed to be surgical failures, about one-quarter (table 1) of the operations being bone fusions which, as pathologists and orthopedists alike have pointed out, can produce a quiescent lesion at best. In many of the thoracoplasty cases, surgery accomplished cavity closure, but the disease in the contralateral lung progressed. In all, there were 65 cases (74.9 per cent) with persistent sinuses, most of which were at the operative site.

There were 11 patients (8 in group A and 3 in group B) in whom the surgical procedure was probably an *important contributory cause of amyloidosis.* These

were the patients in whom massive secondary wound infections developed and who succumbed rapidly to an overwhelming sepsis.

A completely healed condition not having been obtained, the amyloidosis could hardly be expected to resorb in the operated group. If, however, surgery had no influence in preventing the deposition of amyloid, neither did it, except in the above 11 cases, have any effect on its progression. In groups A and B (table 2) the general amount of amyloid throughout the body, estimated from the study of microscopic sections, was about equal, although in group A amyloid was already present at the time of the operation. Since in both groups the underlying disease, the chief factor, was approximately the same in character and extent and the degree of amyloidosis was also approximately the same the added surgical and anesthetic trauma apparently had no augmentative effect.

The degree of amyloidosis in the operated groups varies inversely when compared with a nonoperated group. In table 2 it may be seen that advanced stages of amyloidosis were most commonly encountered in the operated group (55.8 per cent in group A and 65.1 per cent in group B), whereas in 100 unselected

TABLE 2

Extent of amyloidosis

	MINIMAL*	MODERATE†	ADVANCED‡	TOTAL
Group A	7 (16.3%)	12 (27.9%)	24 (55.8%)	43
Group B	6 (14.0%)	9 (20.9%)	28 (65.1%)	43
Unoperated	17 (17.0%)	49 (49.0%)	34 (34.0%)	100

* Amyloid limited to the walls of blood vessels.

† Approximately 50 per cent of the organ replaced by amyloid.

‡ Almost the entire organ replaced by amyloid.

amyloidotic patients upon whom no surgical procedures were attempted the greatest incidence appeared in the moderate group (49 per cent). Except as the surgery increased the number of draining sinuses, this cannot be attributed to the deleterious effects of operation, as in the operated group the underlying disease was usually of longer duration. This generally longer duration is explained partially by the many patients in the operated group with long standing bone tuberculosis and partially by the effect of surgery in prolonging the life of the pulmonary cases.

DIAGNOSIS OF AMYLOIDOSIS

The minimal case of amyloidosis is impossible to detect with our present facilities. Two-thirds of the patients in both groups A and B had clinical or laboratory evidence of amyloidosis (table 3). In the remaining one-third, there was no obvious amyloidosis, the possibility of its presence was not investigated by the congo red test and the amyloidosis was consequently first demonstrated at autopsy. In group A, these cases represent those who died postoperatively within a few days or weeks and who had marked generalized amyloidosis at necropsy; this was certainly present, undiagnosed, at operation.

There were no false negative congo red tests in either groups A or B, when the tests were performed within three months or less of death. The patients listed as having albuminuria were all spilling albumin in large and increasing amounts. In group B, 12 per cent of these were not tested with congo red, a procedure which would probably have explained the albuminuria.

Except for the dye absorption test, we have found all other laboratory tests of little diagnostic value, except as they reflect renal damage. In correlating the data of the entire group of 468 patients, it was found that in only about one-quarter was the blood cholesterol level elevated. The globulin fraction was over 2.8 g. per 100 cc. in only 14.3 per cent. The total protein level, however, was reduced in almost one-half (48.5 per cent), the reduction being due in most cases to loss of albumin in the urine. In a few cases, where the clinical and pathological picture appeared to be dominated by the marked hepatic amyloidosis, the reduction in the albumin fraction occurred with no or little albuminuria. Tiber, Pearlman and Cohen (14) have also noted this discrepancy and have attributed it to the diffuse hepatic injury. Even a partial loss through albuminuria cannot explain all cases of reduced serum proteins, for in only 35.8 per cent of patients were the albumin-globulin fractions equal or their ratios absolutely reversed. Further studies of liver function were not made in a sufficient number of cases to be of statistical importance. The Takata Ara reaction was determined in 29, but no correlation was found between the degree of amyloidosis at autopsy and the strength of the positive Takata Ara reactions.

TABLE 3

Clinical evidence of amyloidosis

	CONGO RED POSITIVE	ALBUMINURIA	HEPATO SPLENOMEGALY	NO EVIDENCE
Group A	22 (51.2%)	17 (39.5%)	9 (20.9%)	15 (34.9%)
Group B	15 (34.9%)	20 (46.5%)	11 (25.6%)	15 (34.9%)

MORTALITY

The underlying infection was the cause of death in more than two-thirds of the group A patients and in 58 per cent of the group B (table 4). In the former, 10 "early" operative deaths are included. Among the entire group of 468 patients, the basic disease was likewise the cause of death in two-thirds and seems to indicate what little effect surgery has on the mortality of the amyloid patient.

TABLE 4

Attributable cause of death

	AMYLOID UREMIA	PARTLY AMYLOID	UNDERLYING DISEASE
Group A	8 (18.6%)	5 (11.6%)	30 (69.8%)
Group B	9 (20.9%)	9 (20.9%)	25 (58.2%)
Total	17 (19.8%)	14 (16.2%)	55 (64.0%)

The cause of death was directly attributable to amyloidosis (amyloid uremia)

in 18.6 per cent and 20.9 per cent instances, respectively (table 4). Although the number of patients is not comparable, it is significant that uremia on this basis was almost twice as frequent in this operated group as it was in the entire group of 468 patients. This again is probably due chiefly to the longer duration of the underlying disease in the operated patients. Those deaths listed as partly due to amyloidosis occurred in those patients with long standing infections, who had marked generalized amyloidosis, usually associated with massive edema and other evidence of the nephrotic syndrome, but without uremia.

The number of "early" postoperative deaths, 32.7 per cent within three weeks and 20 per cent within one week, is obviously far higher than is usual in any series of bone fusions or thoracic operations. However, these are selected "poor risk" patients not only from a general constitutional but also from a pulmonary standpoint and this is not necessarily a significant figure. Of the "early" deaths, 12 of 14 were due directly to "shock" or postoperative spreads, the amyloid being present in such small amounts that it is unlikely that it influenced the ultimate outcome. The remaining 2 patients plus one who died on the fifty-eighth postoperative day had extensive amyloidosis, the relation of which to death is discussed below. (Table 5.)

TABLE 5

Interval last operation and death

	24 HRS. OR LESS	2-6 DAYS	1-3 WEEKS	1-2 MONTHS	3-6 MONTHS	7-12 MONTHS	OVER 1 YEAR
Group A	3	7	4	8	11	5	5
Group B	0	0	0	0	7	13	23

In only one of the "early" deaths was amyloidosis (amyloid uremia) a directly attributable cause of exitus, the operation definitely being injudicious surgery. This person was a 52 year old white man, admitted with albuminuria, edema, elevated nonprotein nitrogen and other evidence of renal damage. These findings were partially attributed to benign hypertrophy of the prostate. A prostatic resection was done, in spite of a positive congo red test. Postoperatively the nonprotein nitrogen rose immediately, the patient lapsed into coma and expired three days later. Since his general condition and renal function had remained essentially stationary for the three months prior to operation, the added surgical insult was undoubtedly responsible for the renal shut-down. The entire clinical picture on admission was typical of amyloid nephrosis and it is doubtful that the prostate was more than a minor factor in the renal insufficiency. Microscopic examination of the kidneys revealed the typical appearance associated with amyloid uremia, a complete blockage of the glomerular capsular spaces by amyloid depositions.

There was one other patient in whom the operative procedure apparently initiated amyloid uremia. This patient had had four stages of thoracoplasty and revision over a three-year period. Since there was still evidence of an open cavity in an apparently functionless upper lobe, a lobectomy was done. The

congo red test three and one-half months before the final operation showed 75 per cent absorption and there was no clinical evidence of amyloidosis. Edema and albuminuria developed within forty-eight hours after operation and the nonprotein nitrogen began to rise one month later. The patient lapsed into coma and expired two months postoperatively. More careful studies of the blood and urine immediately prior to operation would probably have disclosed renal amyloidosis, although it is doubtful that such kidney damage would have influenced the surgical judgment. The 17 patients (table 3) in whom albuminuria was present before operation had no such postoperative evidence of increased renal damage. Six other cases in group A died in amyloid uremia. There was preoperative evidence of varying degrees of renal damage, but the surgical trauma apparently did not influence the ultimate renal shut-down. In none of these did increased kidney damage appear less than one month postoperatively. This interval was usually three to six months, the patients expiring from two and one-half months to three and one-half years after operation.

Since in many patients, amyloidosis of the adrenal is advanced, the involvement of this organ in relation to adrenal insufficiency and operative trauma should be considered. Although none of our cases exhibited frank Addison's disease, such cases have been reported in the literature (Bronfin and Guttman (15)) and the posibility of adreno-cortical insufficiency is always present in a patient with marked amyloidosis.

In 2 of our patients with moderate amyloidosis of the adrenals cortico-adrenal insufficiency was studied by the salt restriction test of Cutler, Power and Wilder (16) before or shortly after operation. In both the test was negative, nor did the postoperative course suggest cortical insufficiency. Of the 14 "early" operative deaths, 2 occurred in patients who had advanced amyloidosis of the adrenals, one being the patient previously described who died in amyloid uremia. The other had a low blood pressure (100/60) before operation and in spite of an extensive mixed infection empyema his temperature for a year before operation was usually low-grade febrile. There was considerable "shock" following thoracoplasty and he expired five days following a Schede operation from "shock" and contralateral spread. A third patient with moderate adrenal amyloidosis, who died six days postoperatively, had previously withstood uneventfully six major thoracic operations. She never completely responded to the usual measures utilized to combat operative "shock," although the last operation was a less formidable procedure than the previous six.

THERAPY

Since the treatment of amyloidosis depends rather upon halting its deposition than upon actual "cure," any therapy contemplated must attack the underlying infection as energetically as possible. Furthermore, while minimal or even moderate amounts of amyloid apparently are of little clinical significance, treatment, particularly if it is surgical, must be undertaken early. Beardsley's (17) interesting case, in which operation was postponed because of the patient's poor condition, but ultimately attempted with complete success, well illustrates the need for early operation. His patient, living and working more than two years

following the last operation, continued to have albuminuria and the possibility of his ultimately succumbing to amyloid uremia is unfortunately not remote. Two of our cases dying in amyloid uremia two and four years, respectively, following operation were similar, although surgery in our cases was not completely successful in eradicating residual sinuses.

Specific treatment of amyloidosis at the present time is impossible. Some support, however, can be given the damaged viscera and this is especially important if surgery is contemplated. Whenever amyloidosis is suspected, determinations of renal, hepatic and adrenal competency should be made. If the required laboratory tests cannot be done, it would be well to assume that these organs are damaged and to institute the appropriate therapy. Except for tests of renal function, available laboratory studies of parenchymal damage are at best quantitatively inaccurate. The amyloid patient should therefore always be given the benefit of replacement or dietary therapy, whether or not specific tests indicate involved viscera.

These therapeutic measures should be directed especially to the liver, kidneys, adrenal glands and to the generally poor nutrition. Protein metabolism in most of this group is inadequate because of many factors, notably hepatic insufficiency, albuminuria, inadequate food intake and poor gastrointestinal digestion and absorption. Throughout the operative period, then, additional protein in the form of amino acids is indicated. During the immediate postoperative period, plasma transfusions, as well as those of whole blood should be helpful. As Elman (18) has pointed out, whenever additional electrolytes, carbohydrates and water are required to maintain daily needs, amino acids are also indicated.

While the salt available in infusions is usually adequate to support adrenal glands moderately involved by amyloidosis, it is probably insufficient for those glands in which advanced damage has occurred. Therefore, at the risk of instituting unnecessary medication in some cases, it would probably be judicious to utilize replacement adreno-cortical therapy in every patient in whom a congo red test is positive, at least during the operative period.

CONCLUSIONS

In order to evaluate the problems of the patient with amyloidosis who is in need of major surgery, we have studied 86 patients, half of whom were operated upon prior to, and half following the development of generalized amyloidosis. There was no marked difference between the two groups either in the number of deaths attributable to amyloidosis or in the amounts of amyloid present. In fact, there were slightly greater amounts of amyloid and a slightly greater number of deaths from amyloidosis in the group which was free of such depositions prior to surgery.

While the operative procedures apparently had little affect on the amyloidosis, the latter may have had some effect on the surgical results, reflected by the 14 deaths in group A which occurred within three weeks of operation. In 2 of these the combination of operative trauma and extensive damage of viscera by amyloid was probably responsible for exitus. In the remaining 12 the cause of death was indubitably the far advanced pulmonary pathological changes. In

other words, except in these 2 cases and one who died two months postoperatively, major surgery was justified in respect to amyloidosis, although the pulmonary disease was apparently too extensive to be operatively remediable.

Resorption of amyloid being only rarely possible, the ideal treatment must be aimed at prevention by eradicating the underlying infection. This must be done either before the amyloid has been deposited or before it has progressed to irreparable visceral damage. For this reason, early diagnosis is essential and every patient in whom control of the basic disease is at all possible should have serial congo red tests performed. When such a test is positive, more energetic treatment is imperative; this, in the tuberculous, usually being surgical. For every additional month which the patient exists with a positive congo red test and uncontrolled basic disease, there is additional amyloid damage, usually irreparable, to his parenchymatous organs.

The decision to operate, therefore, must depend upon whether or not the underlying infection can be controlled. The presence of amyloidosis must be an added indication rather than a deterrent. With evidence of renal or other visceral impairment, surgery becomes obligatory for, although these patients are poor risks, eradication of sinuses and arrest of infection are their only hope of escaping death due to amyloidosis.

The patient with minimal amyloidosis or even moderate, according to our pathological classification, is probably no greater surgical risk than the patient without amyloidosis. When the condition is advanced, however, his chances of surviving the complications which may develop will depend in large measure upon the supportive therapy which can be supplied his damaged viscera.

SUMMARY

The study of the results of major surgery in a group of amyloidotic patients has revealed: (*1*) that the prompt recognition of amyloidosis is essential; (*2*) that amyloidosis is not a contraindication to major surgery; (*3*) that by temporizing with more conservative therapy the opportunity of saving the patient is likely to be lost; and (*4*) that major surgery must be accompanied by energetic supportive treatment of damaged viscera.

For the early recognition of amyloidosis not only the routine use of a single congo red test on every tuberculous patient but serial testing, as well, is essential. As soon as the diagnosis of amyloidosis is made, energetic treatment of the underlying infection is imperative. Even if the more conservative methods of inducing pulmonary rest may, over a prolonged period, arrest the infection, their beneficial effects are likely to take too long to avert an amyloidotic death. The surgical results in this group of "poor risk" patients can certainly be improved if more intensive treatment of the extrapulmonary viscera by amino acids, plasma, whole blood, saline, glucose and adreno-cortical hormone is instituted.

SUMARIO

El estudio del resultado obtenido por la cirugía mayor en un grupo de amiloidóticos reveló que: (1) el reconocimiento rápido de la amiloidosis es indispensable; (2) la amiloidosis no contraindica la cirugía mayor; (3) la contemporización

con la terapéutica más conservadora entraña el riesgo de perder la oportunidad de salvar al enfermo; y (4) la cirugía mayor debe acompañarse de vigoroso tratamiento tónico de las vísceras afectadas.

Para el reconocimiento temprano de la amiloidosis, es indispensable no tan sólo el empleo sistemático de una prueba aislada con rojo del congo en todos los tuberculosos, sino igualmente la comprobación seriada de todos los casos. Apenas se hace el diagnóstico se impone el tratamiento enérgico de la infección subyacente. Aunque los métodos más conservadores de obtener el descanso pulmonar pueden estacionar la infección al cabo de un período prolongado, es probable que el beneficio llegue demasiado tarde para impedir la muerte por amiloidosis. En este grupo de "malos riesgos", puede mejorarse con seguridad el resultado quirúrgico, instituyendo tratamiento más intenso de las vísceras extrapulmonares con aminoácidos, plasma, sangre íntegra, solución salina, glucosa y hormona corticoadrenal.

REFERENCES

(1) Litten, M.: Amyloid degeneration, Heilbarkeiten derselben, Berlin. Klin. Wschnschr., 1885, *22*, 812.
(2) Grigorjeff, A.: Zur Frage der Resorptionsfähigkeit des Amyloids, Beitr. z. path. Anat. u. z. allg. Path., 1895, *18*, 37.
(3) Dantchakow, W.: Über die Entwicklung und Resorption experimentell erzeugter Amyloidsubstanz in den Speicheldrusen von Kraninchen, Virchow's Arch. f. path. Anat., 1907, *187*, 1.
(4) Morgenstern, Z.: Zur Frage über Amyloidosis und Resorption, Virchow's Arch. f. path. Anat., 1926, *259*, 698.
(5) Kuczynski, M. H.: Weitere Beiträge zur Lehre vom Amyloid, Klin. Wehnschr., 1923, *2*, 2193.
(6) Rosenblatt, M. B.: Recovery from generalized amyloidosis secondary to pulmonary tuberculosis, Arch. Int. Med., 1936, *57*, 562.
(7) Reimann, H. A.: Case of amyloidosis with recovery, J. A. M. A., 1935, *104*, 1070.
(8) Walker, G. F.: A case of recovery from amyloid disease, Lancet, 1928, *2*, 120.
(9) Grayzel, H. G., Jacobi, M., Warshall, H. B., Bogin, and Bolker, H.: Amyloidosis, Arch. Path., 1934, *17*, 50.
(10) Pearlman, A. W.: Regression of amyloidosis, Quart. Bull. Sea View Hosp., 1940, *6*, 92.
(11) Metraux, P.: Über Ruckbildungs vorgänge bei menschlicher Amyloidose, Frankf. Ztschr. f. Path., 1929, *37*, 279.
(12) Waldenström, H.: On the formation and disappearance of amyloid in man, Acta chir. Scandinav., 1928, *63*, 479
(13) Stemmermann, M., and Auerbach, O.: The value and limitations of the congo red test for amyloidosis, Am. J. M. Sc., 1944, *208*, 305.
(14) Tiber, A. M., Pearlman, A. W., and Cohen, S. E.: Hepatic function in patients with amyloidosis, Arch. Int. Med., 1941, *68*, 309.
(15) Bronfin, I. D., and Guttman, P. H.: Amyloid degeneration of the adrenals as a factor in producing symptoms of Addison's disease in chronic pulmonary tuberculosis, Am. Rev. Tuberc., 1935, *31*, 1.
(16) Cutler, H. H., Power, M. H., and Wilder, R. M.: Concentrations of chloride, sodium and potassium in urine and blood, J. A. M. A., 1938, *111*, 117.
(17) Beardsley, J. M.: Major surgery in amyloidosis, J. Thoracic Surg., 1943, *12*, 590.
(18) Elman, R.: The practical use of amino acids in protein nutrition, J. A. M. A., 1945, *128*, 659.

HYCODAN[1,2]

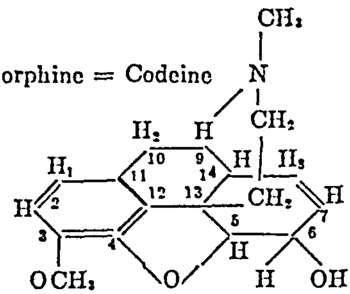
Dihydrocodeinone

PAUL STEIN AND PAUL LOWY

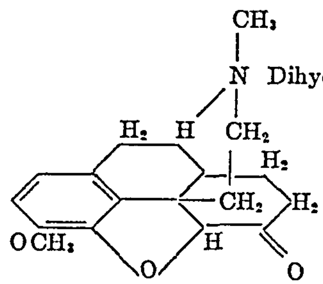
Hycodan, which recently was released for sale in the United States, was produced in order to obtain a cough sedative stronger than codeine but less disagreeable than morphine as far as side-effects and the danger of habituation are concerned.

Hycodan is the bitartrate salt of dihydrocodeinone. The latter has been used in Germany under the name Dicodid. It received favorable reports in German medical literature.

Methylmorphine = Codeine



Dihydrocodeinone = Hycodan



As the structural formulae show, dihydrocodeinone differs from codeine, that is, methylmorphine, by a change at the C6-atom. There the alcoholic hydroxyl group is replaced with a ketonic oxygen, so that Hycodan belongs to the morphine ketone types, of which Dilaudid (dihydromorphinone) is another example. Such changes at the C6-atom of the morphine formula generally strengthen the potency of a morphine derivative, thus intensifying the characteristic physiological and toxic morphine actions, while at the same time shortening the duration of the drug effects. Yet dihydrocodeinone differs from the morphine and codeine formulae also in another respect. It is a hydrogenated codeinone. While the replacement of the hydroxyl group at C6 by a keto-oxygen effects increased activity (implying stronger sedative and analgesic action), the removal of the adjacent double bond by addition of two H-atoms effects reduced toxicity and again increased analgesic action. These effects of hydrogenation have been demonstrated in animal experiments by Eddy (1) and Eddy and Reid (2). It was shown in cats that the ratio of the analgesic dose of dihydrocodeinone to that of codeine is twice as great as the ratio of the respective toxic doses.

These pharmacological characteristics give Hycodan a favorable position among the morphine derivatives. A brief survey of its actions on various organs and systemic functions may now follow.

EFFECT ON RESPIRATION

Pharmacological studies and clinical experiences indicate that Hycodan does

[1] From the Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases, New York, New York.

[2] Hycodan was supplied for this study by the courtesy of Endo Products, Inc., Richmond Hill, New York.

not depress the respiratory centre to such a degree that its therapeutic usefulness as a cough remedy and as a general sedative would be impaired by its depressant action. In therapeutic doses it works as a respiratory sedative, like morphine which, in doses up to 15 mg., quiets rapid and deepens shallow breathing. Wright and Barbour (4), who studied the respiratory effect of morphine and several of its hydrogenated derivatives in rabbits, found the minimum effective dose reducing the respiratory activity to be for morphine 0.32 mg. per kilogram, and for dihydrocodeinone 0.21 to 0.3 mg./kg. They recorded the respiratory rate, the minute volume and the sensitivity to stimulation by carbon dioxide.

As we shall see later, a Hycodan dose of 5 to 10 mg. is required in clinical use. The usual dosage of morphine for the sedation of cough and pain is 10 mg. Thus comparing the respiratory activity and the therapeutic doses of morphine and Hycodan, the latter does not appear to be a considerably more active depressant of respiration, in spite of the general increase in its activity as usually associated with changes at the C6-atom of the morphine structure; and it does not require a dosage which would affect respiration more than the average morphine dose.

CARDIOVASCULAR AND GASTROINTESTINAL EFFECTS

The effect of Hycodan upon the cardiovascular system is insignificant, like that of other morphine derivatives, as long as therapeutic doses are employed. The morphine alkaloids stimulate the vagus centre and thereby the vagal inhibitory actions. Therapeutic doses slow the rate and increase the fulness of the pulse. Higher doses produce not only bradycardia but also conduction disturbances, as was shown experimentally. German workers used dihydrocodeinone in doses up to 20 mg., and also by injection. They did not report any cardiovascular disturbances.

The nauseant and emetic effect of morphine and its related drugs which is caused by their action upon the vomiting centre, but also by a pylorospastic action, is well enough known. In larger doses morphine and its derivatives work as anti-emetics. Early German reports emphasizing that dihydrocodeinone has slight gastrointestinal side-effects appear substantiated by the studies of Eddy and Reid. These workers compared morphine, dihydromorphinone (Dilaudid) and dihydrocodeinone. While the other drugs produced vomiting in small doses and, after an apomorphine injection, suppressed it in five to ten times stronger doses, dihydrocodeinone, though producing nausea, did not cause vomiting over the range of the dosage employed. Yet a relatively low dose of dihydrocodeinone was found which completely suppressed the emetic effect of a preceding apomorphine injection. These experiments, performed in cats and dogs, showed that dihydrocodeinone has a relatively slight stimulating effect on the vomiting mechanism, while being capable of depressing it markedly.

The pylorus as well as the intestinal musculature responds to morphine alkaloids with a tonic spasticity. This, along with a slowing of the rhythmic and propulsive movements and with a decrease of gastric, pancreatic and biliary secretion, impairs the absorption of foodstuffs and the expulsion of the feces. No pharmacological evidence seems to be available proving that Hycodan has a weaker intestinal effect than morphine. However, the clinical reports of Roller

(5), Schindler (6) and other German observers assert that no constipative effect resulted from the administration of dihydrocodeinone. In our own clinical experience the constipative effect of Hycodan appeared much weaker than that of morphine and certainly not stronger than that of codeine.

ADDICTION LIABILITY

The evaluation of any morphine derivative must be concerned with its addiction liability. Himmelsbach (7, 8), among other workers, has studied clinically the dependence action of a large series of morphine and codeine derivatives representing various important structural changes of the morphine molecule. With none of the employed derivatives did he find a definite decrease of the potency or duration of the dependence action. In another paper Himmelsbach (9) proved that not even codeine can be considered a nonaddicting drug, though many physicians seem to think so.[3]

Hycodan does not seem to occupy an unfavorable position among the morphine alkaloids as far as habituation is concerned. Eddy and Reid (2), in experiments with dogs and monkeys, found that dihydrocodeinone did not develop any noticeable tolerance before the ninth week of the experiment. Only then had the dose to be increased in order to reëstablish the initial depressant effects. In contrast to this, the initial effects of morphine, and similarly of dihydromorphinone (Dilaudid), disappeared after eight days of drug administration as a result of acquired tolerance. Higher doses did not reproduce the drug symptoms in proportion with the increase of the dosage; and the symptoms again subsided after only six days of continued treatment. Withdrawal symptoms were least with dihydrocodeinone

Since both the increase of dosage due to acquired tolerance and the severity of withdrawal (abstinence) symptoms are essential factors in the development of drug addiction, these animal experiments seem to indicate that Hycodan does not possess a high addiction liability. Clinical experiences in man are in accordance with these animal experiments.

CLINICAL REPORTS

Clinical reports on dihydrocodeinone appeared in German literature under the name Dicodid. Schwab and Krebs (10) found it satisfactory as a cough sedative in cases of pulmonary and laryngeal tuberculosis, chronic bronchitis and bronchitis of congestive heart failure. The amount of sputum was not reduced by the drug. Two daily doses of 10 mg. also assured a quiet night's sleep. Pain was well relieved in bronchial carcinoma, pneumonia and syphilitic aortitis. While these observers have not seen signs of habituation, Hecht (11) noted euphoric action and habituation symptoms. Hecht otherwise reports that his patients preferred dihydrocodeinone to codeine and found it more effective in cough sedation than eucodal, paracodine and pantopon. Castelhun and Lang-

[3] He used codeine as a substitute after withdrawal of morphine. No abstinence symptoms appeared. They set in however when codeine, too, was abruptly discontinued. Then the clinical picture "was not different remarkably from that seen after abrupt morphine deprivation."

heinrich (12) obtained complete sedation of cough in all their cases and the effect of dihydrocodeinone on pain was equal to that of morphine, both as to degree and duration of the effect. They emphasize the rarity of pylorospastic symptoms after the use of this drug. Roller (5) and Schindler (6) were completely satisfied with the cough sedation and have never observed a constipative effect. When taken during the day, the drug never produced drowsiness and fatigue. Schindler (6) used it for pre-endoscopic sedation. Ambulatory patients were able to walk home after their endoscopy when dihydrocodeinone had been injected. This they were unable to do after morphine or pantopon sedation.

OUR OWN CLINICAL EXPERIENCES

Hycodan has been used since March, 1943 in the Division of Pulmonary Diseases in Montefiore Hospital. The total number of Hycodan tablets dispensed in the Hospital between March, 1943 and May, 1945 is 13,000 tablets of 0.005 g. each. No toxic or notably harmful effect has been reported. Our first observation of the clinical effects of Hycodan was based on (*1*) the recordings by the nurses on the patients' charts, (*2*) the statements of the patients, (*3*) impressions gained by our house-staff physicians. This first observation comprised 26 patients who received Hycodan between March, 1943 and March, 1944. The diagnoses of these cases were: chronic exudative or fibrocavitary pulmonary tuberculosis, 11 cases; chronic fibrocavitary pulmonary tuberculosis with tuberculosis of the larynx, 2 cases; chronic pulmonary tuberculosis with empyema, 2 cases; chronic fibrotic pulmonary tuberculosis with emphysema and asthmatoid bronchitis, 2 cases; bronchiectasis, 2 cases; bronchogenic carcinoma, 6 cases; Boeck's sarcoidosis, one case.

Appraising the Hycodan effect on cough, we found it completely satisfactory in 27 per cent of our cases. In 58 per cent of the cases, we classified the effect as markedly better than that of the preceding medication (codeine, dionin or Dover's powder); we found it only fair, but still more effective than the previous medication had been, in 15 per cent of our patients. In no case was the cough sedation by Hycodan, compared with other cough sedatives used before, less effective or only equal. It is, for instance, certain that Hycodan in a dosage of 5 to 10 mg. was more effective than codeine in a dosage of 30 to 60 mg., or dionin in a dose of 15 to 22.5 mg. Patients told the house physicians that Hycodan helped their cough when codeine had become unsatisfactory.

When taken at night, Hycodan also seemed to improve sleep. Its effect on dyspnea equals the helpful action, by central sedation, of morphine and other related drugs. In asthmatics, however, the value of these drugs is always dubious and this applies to Hycodan as well; bronchospasm is not alleviated by morphine alkaloids; their merit in the relief of asthma, when combined with epinephrin, is due to central sedation and possibly to some suppression of bronchial secretion.

No drowsiness was noted in this series when Hycodan was taken during the day. We have not observed any euphoric action and in none of our cases could habituation or dependence be noted during the period of observation. The drug

was taken for periods of several months to one year. Intermittent administration of other drugs was well accepted by the patients. The single dose was 1 to 2 tablets, that is, 5 to 10 mg., and never higher; continued administration never required increasing dosage.

We did not give Hycodan by injection. On oral administration, no habit formation was observed. Not only codeine, but also barbiturates and other drugs free of opiates could be substituted for Hycodan and this substitution was always well accepted by the patients. One patient refused to resume codeine after the use of Hycodan; but this appeared justified by his explanation that codeine had not helped him as well as Hycodan. Yet we want to emphasize that neither the methods used in clinical observation nor the duration of our test period could serve as sufficient evidence to pronounce Hycodan a non-habit-forming drug. As shown before, none of the morphine derivatives in use is really non-addicting. Hycodan, however, has the advantage of a relatively low addiction liability.

No toxic effects were noted in this series of cases. This agrees with the German reports. The German clinicians used a maximum dose of 20 mg. in exceptional cases, and Schindler considers this the highest permissible dose. It sometimes caused not drowsiness, as might be expected, but a state of excitation.

No constipative effect of Hycodan was recorded in any of these 26 patients and no laxatives were necessitated by its use. One patient who had been constipated under codeine treatment did not need laxatives any more when Hycodan was given for his cough sedation.

After the follow-up of these 26 cases we selected the small number of 9 cases for a closer study of Hycodan effects. In this series, one of us (P. L.) saw and examined every case personally and regularly and all pertinent signs and symptoms were recorded daily throughout the twenty-three-day period of observation. For the purpose of comparison, the patients were observed (*1*) when no cough sedative was given; (*2*) when codeine, (*3*) when Hycodan was taken. A second codeine period followed, so that we and the patients were better able to compare effects of codeine and Hycodan and also in order to ascertain that codeine, when resumed after a period of Hycodan medication, was not less effective than before.

The results of this close observation are summed up in table 1. Doses of codeine or Hycodan are not mentioned in this table. However, it is to be understood that in every case the dosage of Hycodan was one-third of the codeine dosage, so that 0.01 g. Hycodan was taken by patients whose codeine dose had been 0.03 g.; and 0.015 g. Hycodan was substituted for 0.045 g. codeine. Several patients have received codeine by injection, while Hycodan was given exclusively by the oral route. This probably, to some degree, gave an advantage to codeine in its comparative effect.

According to our table, the weaker Hycodan dose was superior to the stronger codeine dose in 6 of the 9 patients as far as the relief of cough is concerned. No difference in the effect on sleep was observed.

The amount of sputum was considerably influenced by both drugs, with the exception of one patient in whom the reduction of expectoration was insignificant.

TABLE 1

Patient	Cough without medication [moderate—irritating—severe]	Relief of cough (in per cent of days of treatment) [slight—satisfactory—complete]		Sputum (daily average in cc.)			Sleep [moderately—severely—not disturbed]			Day time sedation [none—slight—marked]	
		From codeine	From hycodan	Without medication	With codeine	With hycodan	Without medication	With codeine	With hycodan	On codeine	On hycodan
L. T. 50 years	Moderate to severe	100 satisfactory	10 slight 90 satisfactory	200	125	105	Not disturbed	Not disturbed	Not disturbed	Slight	3 days marked, later slight
E. D. 55 years	Severe	100 satisfactory	100 complete	250	85	55	Moderately to severely disturbed	Not disturbed	Not disturbed	None	Marked
D. S. 61 years	Moderate	20 satisfactory 80 complete	100 complete	100	45	40	Not disturbed	Not disturbed	Not disturbed	None	1st day marked, later none
T. R. 32 years	Irritating to severe	20 slight 80 satisfactory	10 slight 90 satisfactory	110	105	100	Moderately to severely disturbed	Not disturbed	Not disturbed	None	None
T. R. 59 years	Moderate to severe	100 satisfactory	90 satisfactory 10 complete	65	25	25	Not disturbed	Not disturbed	Not disturbed	None	4 days marked, later none
I. S. 39 years	Moderate to severe	20 slight 80 satisfactory	30 slight 70 satisfactory	245	155	155	Severely disturbed	Not disturbed	Not disturbed	None	None
N. S. 21 years	Irritating	40 satisfactory 60 complete	20 satisfactory 80 complete	300	225	230	Not disturbed to severely disturbed	Not disturbed	Not disturbed	Slight	Slight
H. H. 26 years	Irritating	70 satisfactory 30 complete	50 satisfactory 50 complete	50	30	30	Not disturbed	Not disturbed	Not disturbed	None	Slight
S. S. 53 years	Irritating to severe	10 slight 80 satisfactory 10 complete	20 satisfactory 80 complete	75	45	35	Severely disturbed	Not disturbed	Not disturbed	None	None

In 4 of the remaining 8 cases the amount of sputum was more markedly reduced by Hycodan than by codeine. We do not believe that this can be ascribed to sputum retention. Such marked retention would most likely have caused fever within a few days and would also have caused our "experienced" patients to complain of troubles associated with insufficient expectoration. Actually only one patient felt "tight" and this occurred on codeine. The fact that morphine derivatives are known to be suppressors of bronchial secretion obviously accounts, at least to a large degree, for this remarkable reduction of sputum.

The sedative effect of Hycodan, beside the sedation of cough, appeared stronger than that of codeine. One patient felt slightly drowsy. Four of the 9 patients experienced a marked day-time sedation when taking Hycodan which, however, was present only during the first four days of Hycodan treatment in one patient, during the first three days in one patient, and only on the first day in another one. The one patient who felt "slightly drowsy" showed marked day-time sedation throughout the period of Hycodan administration.

No notable effects on temperature, blood pressure and pulse rate could be observed in any case, either on codeine or on Hycodan.

No unusual symptoms occurred except "a feeling of warmth and perspiration" which was reported by 2 patients on the first day of Hycodan administration, but not subsequently. No nausea occurred, whether codeine or Hycodan was taken.

As regards constipation, our impression that Hycodan has no significant constipative effect has been verified by the close follow-up of these 9 patients. In no instance did constipation develop at any time during the period of Hycodan administration. One nonconstipated patient became constipated on codeine but was free of it on Hycodan. One patient had been constipated not only while taking codeine but also while he was kept without any medication.

SUMMARY

Hycodan (dihydrocodeinone bitartrate) can be characterized pharmacologically as a more active analgesic and cough sedative than codeine, but a less active one than morphine. It shows a favorable ratio between analgesic and toxic effects and has a relatively low addiction liability. In therapeutic doses, it does not produce vomiting and its constipative effect appears to be insignificant.

Hycodan has been used on the wards for pulmonary diseases in Montefiore Hospital. The clinical results are in accordance with the pharmacological reports. Hycodan proved to be highly effective in sedation of cough and in the alleviation of pain.

SUMARIO

Farmacológicamente, puede caracterizarse al "Hycodán" (bitartrato de dihidrocodeinona) como un analgésico y sedante antitusivo más activo que la codeína, pero menos que la morfina. Dotado de un equilibrio favorable entre los efectos analgésico y tóxico, muestra relativamente poca propensión a engendrar narcomanía. A dosis terapeúticas no produce vómitos y su efecto astringente parece ser insignificante.

El "Hycodán" ha sido utilizado en las salas dedicadas a afecciones pulmonares

en el Hospital Montefiore, concordando el resultado clínico con los informes farmacológicos. La droga resultó ser muy eficaz para calmar la tos y aliviar el dolor.

REFERENCES

(1) Eddy, N. B.: J. Pharmacol. & Exper. Therap., 1934, *51*, 35.
(2) Eddy, N. B., and Reid, J. G.: J. Pharmacol. & Exper. Therap., 1934, *52*, 468.
(3) Robbins, B. H., Fitzhugh, O. G., and Baxter, J. H., Jr.: J. Pharmacol. & Exper. Therap., 1939, *66*, 216.
(4) Wright, C. I., and Barbour, F. A.: J. Pharmacol. & Exper. Therap., 1935, *53*, 34.
(5) Roller: München. med. Wchnschr., 1924, *71*, 648.
(6) Schindler, R.: München. med. Wchnschr., 1923, *70*, 467.
(7) Himmelsbach, C. K.: J. Pharmacol. & Exper. Therap., 1939, *67*, 239.
(8) Himmelsbach, C. K.: J. Pharmacol. & Exper. Therap., 1941, *71*, 42.
(9) Himmelsbach, C. K.: J. A. M. A., 1934, *103*, 1420.
(10) Schwab, E., and Krebs, W.: München. med. Wchnschr., 1924, *71*, 1363.
(11) Hecht, P.: Klin. Wchnschr., 1923, *1*, 1069.
(12) Castelhun and Langheinrich: München. med. Wchnschr., 1924, *71*, 1610.

DEPTH GROWTH OF ACID-FAST BACILLI IN LIQUID MEDIA[1]

I. Technique

W. F. DREA

Certain strains of acid-fast bacilli will grow in the depth of a liquid synthetic culture medium when as little as 10^{-7} to 10^{-8} mg. of the bacilli are planted.

The growth of tubercle bacilli when submerged in a liquid culture medium more nearly approximates the growth of the bacilli in living animal tissues than does growth on the surface of a medium exposed directly to the atmosphere.

It would appear, therefore, that depth culture experiments in liquid synthetic media are of importance in the search for any required accessory growth factors for certain already established strains of tubercle bacilli and especially for the growth of bacilli directly from tuberculous tissues and sputa.

Also, depth culture studies of probable chemotherapeutic agents added to liquid synthetic media as well as to more complex media such as blood serum or to mixtures of liquid synthetic media and serum or other complex biological substances should be of value.

In the remainder of the paper "liquid synthetic medium" will be referred to as S.M. and, unless otherwise stated, Long's (1926) is implied.

Calculated amounts of the bacilli ranging from 10^{-1} to 10^{-8} mg. are dropped into the S.M. If, after sufficiently long incubation at 37°C., only considerably larger amounts of bacilli yield growth in the S.M. than on egg-yolk media, such as Corper's (1933), a search using this technique can be made for the growth promoting factor or factors in the egg-yolk.

Antibacterial properties of various substances can be similarly investigated; the complex with known, unknown or unrecognized chemical molecules and the chemical compounds with well defined structures. In this way, some information may be secured about probable chemotherapeutic agents. A preliminary study can be made by determining the smallest concentration of the material in decimal dilutions in the S.M. that will prevent growth of a known amount of bacilli, the same amount of bacilli growing in the next weaker decimal dilution and in the control medium. If more detailed studies are indicated, concentrations between the decimal dilutions preventing and permitting growth can be prepared and amounts of bacilli ranging from 10^{-1} to 10^{-8} mg. planted in this as well as in the controls. This method of antibacterial investigation was employed by Drea (1944) who used the H37 strain of bacilli. One advantage of planting 10^{-3} mg. of bacilli of the H37 strain in 20 ml. of Long's S.M. is that 1 ml. of this agitated planted medium containing about 5×10^{-5} mg./ml. may be retransplanted to fresh S.M. and produce growth. Therefore, the bactericidal as well as the bacteriostatic properties of added substances can be readily determined for a strain of bacilli such as H37 which consistently produces growth when amounts

[1] From the Laboratory of the Colorado Foundation for Research in Tuberculosis at Colorado College, Colorado Springs, Colorado.

as small as 10^{-7} mg. are planted in the S.M. Since 10^{-3} mg. of bacilli represent about 10^{6} bacilli, it would appear that we have here a sufficiently large number of well dispersed bacilli to work with at least in preliminary studies. Heavier suspensions than 10^{-3} mg./ml. are likely to have more and larger clumps of bacilli and these together with the larger number of bacilli, if much more than 10^{-3} mg. bacilli are planted, may interfere with the findings. On the other hand, it may be desirable to plant considerably less than 10^{-3} mg. of such a strain as H37 not only in antibacterial but also in growth promoting factor studies.

Improperly cleaned glassware or the introduction of very small amounts of extraneous contaminating substances into thoroughly cleaned glassware may prevent the growth of small numbers of the bacilli at the bottom of the S.M., even though relatively large numbers of the bacilli grow under the same conditions (Drea, 1942). It seems desirable to describe the techniques now used by the writer after five years of this kind of investigation.

CLEANING OF GLASSWARE

All glassware that has been in contact with bacilli is sterilized in the autoclave. The pyrex Erlenmeyer culture flasks are then rinsed vigorously with hot tap water to rid them of gross amounts of bacterial cultures. The rinsing also tends to wash away any substances, antibacterial or growth promoting, that may have been added to the culture medium. Flasks containing agar, pectate, paraffin, etc., are cleaned separately from those not containing them. The flasks are then immersed in a hot water solution of the following: 0.7 per cent sodium metasilicate (Metso Granular), 0.07 per cent tetra sodium pyrophosphate and 0.07 per cent trisodium phosphate. It will be noted that this cleaning solution contains no aliphatic carbon chain compounds such as soaps, some of which when present in very small amounts in S.M. can prevent the growth of small numbers of tubercle bacilli (Drea, 1944). The detergent solution with the immersed flasks is brought to boiling point (92°C. at the altitude of this laboratory) for one hour, and then allowed to cool to room temperature. After about twenty-four hours, cold tap water is run into the enameled pail, to float out the loosened debris, paraffin if present, etc. The flasks are then removed, rinsed four times with cold tap water and inverted to dry.

All other glassware with the exception of the pipettes is similarly cleaned.

The prolonged immersion of the glass in the detergent solution at room temperature following the boiling period not only helps in the cleaning process but also should help to remove substances previously "dissolved" or adsorbed by the glass.

The glassware, following the above treatment, is very clean and requires no swabbing of the inner walls. Our tap water contains only small amounts of dissolved material and it has not been necessary to make the final rinsings with distilled water for much of the work done by the writer. If the tap water is very "hard" it may be "softened" with Zeolite as advised by Gaddis (1942) or it may be deionized with synthetic resins as exchange adsorbents (Gaddis and Kubina, 1943).

Where indicated, the final rinsings should be done with distilled or redistilled water.

The required actual working time for the described cleaning is no greater than is necessary for what is usually considered good cleaning.

In certain types of investigations it may be advisable to use acid oxidizing solutions for cleaning the glassware.

The $HNO_3 + H_2SO_4$ mixture recommended by Tobie (1941) and the $KNO_3 + H_2SO_4$ solution advised by Laug (1934) are very effective. They have the merit of not introducing Cr into the glassware as happens when dichromate acid solutions are used. There have been reports calling attention to the harmful effects on the growth of organisms by Cr retained by glassware cleaned with dichromate acid solutions (Richards, 1935). The writer, influenced by these reports and also by the cardinal rule that even traces of substances not planned for in culture media should not be knowingly introduced in such studies as these if they can be avoided, depended, during his earlier work, solely on the HNO_3 mixtures when acid cleaning was thought to be desirable (Drea, 1942).

The HNO_3 solutions are objectionable because they give off harmful fumes when heated or when water is added as in rinsing. Proper precautions may be taken against the fumes but it may be inconvenient, especially when large numbers of pieces of glass are to be treated. For this reason it was decided to investigate the effect of Cr on the growth of the H37 strain in S.M.

Each of the following was investigated by itself after adding it to the S.M.: acid cleaning solution (500 ml. of a saturated solution of $K_2Cr_2O_7$ in water and 800 ml. of concentrated crude H_2SO_4), CrO_3 and $K_2CR_2O_7$. It was found that 10^{-1} per cent of the dichromate acid solution, 10^{-1} per cent CrO_3 and 10^{-2} per cent $K_2CR_2O_7$ permitted growth from 10^{-3} to 10^{-8} mg. of H37 bacilli and 10^{-1} per cent CrO_3 and $K_2CR_2O_7$, respectively, prevented growth. Treating the culture flasks with the dichromate acid solution as in cleaning and then rinsing with water resulted in no inhibition of growth from the smallest number of bacilli planted, the results being the same as for the flasks treated with the HNO_3 solution.

It is apparent that no growth inhibition of the H37 *strain* results from dichromate acid cleaning of the culture flasks. While the possible cumulative effect of Cr from repeated growth experiments and dichromate acid cleanings has not been especially investigated, no indication of it was noted during one period when this method of cleaning was employed. It would seem that the prolonged immersion of the flasks in the detergent solution previously referred to would counteract any tendency to cumulative adsorption or dissolving of Cr by the glass.

The flasks either before or immediately after drying may be tested for cleanness by filling them with hot tap water. If they are clean no gas bubbles will adhere to the glass walls. Adherence of glass bubbles is evidence that the inner glass walls are not clean. Another test is to place about 5 cc. of hot water in a cool dry flask. If the glass is clean, no vapor will condense as very small drops producing a vapor pattern on the cooler wall above the hot water. Also, if the rounded freshly flamed end of a glass rod be rubbed against the clean glass surface, a scratching sound and resistance to the rubbing will be very noticeable. A

striking example of an invisible organic film adsorbed on a glass wall is evidenced by taking an Erlenmeyer flask that answers the above mentioned requirements for cleanness, plugging it with cotton and heating it to about 150°C. in a hot air oven. Tests will demonstrate on the inner wall an organic film produced by adsorption of distillates from the cotton.

The washed and dried pipettes are cleaned by immersing them in the HNO_3 + H_2SO_4 mixture at room temperature for twenty-four hours and then washing with water.

TECHNIQUE FOR PLANTING AND GROWING THE BACILLI

Twenty ml. of S.M. are placed in 50 ml. pyrex Erlenmeyer flasks which are then covered with loosely fitting aluminum or pyrex glass caps, preferably the latter. The aluminum caps were cleaned by boiling for one hour in a 0.1 per cent solution of sodium metasilicate, allowing them to be immersed for twenty-four hours in this solution at room temperature and finally rinsing with water. The medium is then autoclaved at 115 to 120°C. for fifteen to twenty minutes.

For greater accuracy, sterile S.M. is measured directly under aseptic conditions into dry flasks previously sterilized in the autoclave.

Substances to be investigated for their growth effects are dissolved in watery solutions, made sterile if they cannot be prepared as aseptic solutions, and added to the sterile S.M. in the flasks.

Careful preparation should make readjustment of the pH (7.2) unnecessary.

The bacilli are now planted.

After planting, the tops of the culture flasks are covered with flamed aluminum foil of 0.0004 inch or slightly greater thickness, which is folded loosely over the top and neck of the flask. A small tightly embracing rubber band is placed over the foil just beneath the rim. The foil is then molded tightly over the rim and neck of the flask. Because there may be pin-point holes in the foil, it is advisable to smear the top surface of the foil with melted paraffin of 68 to 70°C. melting point. There will be very little evaporation during prolonged incubation. However, if the foil is covered all over with the paraffin and the margins sealed to the glass, growth will take place and this is done when agar or pectate has been added to the synthetic medium. Another good means to prevent evaporation is to place a Cel-O-Seal thimble over a 0.0006 inch aluminum foil cap. In one experiment where this was done, the Cel-O-Seal (du Pont de Nemours) thimbles were rinsed first with distilled water, in order to free them of glycerol before placing them in position. After drying, the thimbles gripped the necks of the flasks, squeezing tightly on the aluminum foil. Very few of the thimbles cracked, the evaporation was nil and the growth from the smallest numbers of bacilli was good.

Cotton stoppers are not used. It was reported by Drea (1942) that growth inhibiting distillates from nonabsorbent cotton stoppers prevented the growth of small numbers of bacilli from the H37 strain. This was especially true when the flasks with the cotton stoppers were sterilized in the hot air oven. There is also the hazard of dropping cotton debris into the medium which is objectionable in such studies. Impregnating the cotton with paraffin is objectionable, because

paraffin vapors may combine or mix with cotton vapors to form objectionable additions to the S.M.

PREPARING SUSPENSIONS OF BACILLI FOR PLANTING

The rounded end of a pyrex glass rod of about 28 x 1 cm. dimensions is ground by means of medium coarse carborundum powder against the concave bottom of a pyrex tube of 1.5 x 12.5 cm. outside dimensions. The resulting pestle-mortar effect is good for grinding the bacilli, which is done by hand rotation of the rod. The bacilli are generally taken from a surface culture on Long's liquid medium. Excess moisture is removed by placing the bacilli on well washed sterile filter paper in a sterile Petri dish. About 6 mg. are weighed accurately to within 0.1 mg. in the grinding tube. The bacilli are ground at first with the grinding end of the rod slightly moistened with 10^{-1} per cent NaOH in water. This NaOH solution is an excellent dispersing agent for tubercle bacilli and also has the merit of not introducing ions or molecules not already present in the S.M. One drop is added to the bacilli and careful grinding is done to disperse the bacilli as much as possible. A second drop is added and the same process is repeated. Other drops are added intermittently followed by grinding until 7 or 8 drops have been placed in the tube. Sufficient 10^{-1} per cent NaOH solution is now added to make a suspension of 1 mg./ml. The succeeding decimal dilutions are made with distilled water in the suspension tubes. A different clean 1 ml. pipette is used to transfer each bacillary suspension to be diluted. Use of the same pipette for making all of the diluted suspensions may result in serious errors. The plantings are made by dropping into the culture medium 3 drops (0.1 ml.) of the suspended bacilli from a calibrated Pasteur pipette (Fildes, 1931).

The amount planted will then be one-tenth of that present per ml. in the suspension. For example: 0.1 ml. of an estimated 10^{-7} mg./ml. suspension will give approximately 10^{-8} mg. bacilli planted and with the H37 strain about 50 per cent of such plantings result in growth.

With vanishing small numbers of bacilli per ml. of the suspension, there will necessarily be no bacilli present in some of the small samples planted and one or a few bacilli in others. Therefore, there will be discontinuities of growth, some samples resulting in growth and others in no growth. This was pointed out by Berg (1941) and demonstrated by Drea (1940, 1942).

Growth, when it takes place, always begins at the bottom of the liquid synthetic medium. Later, there will be surface growth in addition to the bottom growth in 100 per cent of the 10^{-1} to 10^{-5} mg. plantings inclusive, of the H37 strain. In the last 49 experiments, 17 of the 10^{-6} mg., one of the 10^{-7} mg. and none of the 10^{-8} mg. plantings produced surface growth. All of the plantings down to and including 10^{-7} mg. resulted in growth. The 10^{-8} mg. plantings produced growth from 24 out of the last 49 plantings, which approximates the 21 out of 40 other similar plantings resulting in growth previously reported by Drea (1942).

If it should be desirable to secure bottom growth only, two methods may be used for H37 bacilli. The first is to plant 10^{-6} mg. in a number of flasks when about 65 per cent will have no surface growth or 10^{-7} mg. when practically all of

the plantings produce only bottom growth. The second method is to let 2 drops of a sterile mineral oil fall on the surface of the S.M. after it has been planted. The oil will prevent surface growth from even 10^{-1} mg. plantings and at the same time permit good growth at the bottom. This amount of oil will permit growth at the bottom of the medium from the smallest plantings of 10^{-7} to 10^{-8} mg. H37 bacilli that will grow when it is absent.

DISCUSSION

The importance of using synthetic culture media in the study of required accessory growth factors is self evident. An illustration of this is provided by the H37 strain. Egg-yolk media permit growth from as little as 10^{-8} mg. of these bacilli. The S.M. to which about 2 per cent agar has been added will allow growth only when amounts greater than about 10^{-3} mg. are planted, smaller plantings resulting in no growth. An explanation for this was that the egg-yolk contained growth factors not present in the synthetic medium, and that the large plantings that did grow on Long's medium plus agar carried over sufficient growth promoting factors from the parent culture or were able to generate them. The reason for using agar was that it was thought to be inert and provided a firm surface for the planting of the dispersed bacilli which were not considered capable of growth at the bottom of the liquid S.M. It was known that small numbers of yeast cells would not grow in a culture medium that permitted larger plantings to grow. However, a synthetic medium to which agar has been added is no longer a synthetic medium only, because of the highly complex and unknown substances in the agar. Furthermore, the agar when added to Long's medium does not permit growth from less than about 10^{-2} mg. of the H37 strain, when all of the conditions set forth for the successful growth of about 1/100,000th of this amount in the liquid medium without agar are observed. The growth on the agar medium from the smaller productive plantings was also characterized by the absence of haphazard distribution, such as should result from chance distribution of the planted bacilli. It was this last named fact that, in the earlier stage of this work, in part, pointed to the probable inability of well dispersed and isolated bacilli to multiply on the agar and S.M. surface, when they might grow in the S.M. without agar. Because the H37 strain will produce growth in the liquid S.M. when vanishing small numbers of bacilli are planted, it appears safe to conclude that this strain does not require added growth factors although they may make the growth more rapid or more profuse.

But there are strains of tubercle bacilli that do not grow in Long's S.M. from such small numbers of bacilli as grow on egg-yolk media and it is for these that accessory growth factors may be sought.

Emphasis has been placed upon the necessity of very clean glassware and the importance of keeping out extraneous substances such as distillates from cotton stoppers. When this work was first attempted, the pyrex culture flasks were new and nonabsorbent cotton stoppers were used. The cleaned dry flasks and stoppers were sterilized in the hot air oven at 150 to 160°C. for one hour. The S.M. was placed in the flasks, the stoppers were replaced and the flasks with their

contents were autoclaved at 120°C. for twenty minutes. The bacilli were then planted, the cotton stoppers were lightly impregnated with paraffin of about 54°C. melting point and incubation was started. It was under these conditions that it was discovered that the H37 strain would grow at the bottom of the S.M. from plantings at least as small as 10^{-6} mg. (Drea, 1940). Irregular and nonconstant growth was secured from smaller plantings. The flasks at the end of a growth experiment were autoclaved, cleaned by the usual methods then used and again treated as before for further growth studies. After some time it was noted that growth was being limited to plantings anywhere between 10^{-7} and 10^{-2} mg. and that growth inhibiting substances were then present that previously were absent. Because the growth inhibition was gradual in its intensity of development, it was concluded the glass had gradually acquired, by adsorption, invisible organic films that inhibited the growth of small numbers of the bacilli. Plantings of 10^{-2} mg. consistently grew and it was evident that sufficiently large numbers of bacilli could counteract the poison. When the same flasks were made especially clean it was demonstrated that growth would occur almost without exception from 10^{-7} mg. plantings and from about 50 per cent of 10^{-8} mg., provided cotton stoppers impregnated with paraffin were not used. The inhibition was greatest when the flasks with the cotton were heated in the hot air oven and least when only autoclaved.

The conclusion that the nonabsorbent cotton distillates were harmful was based on the following findings. Acid cleaned flasks with nonabsorbent cotton stoppers were heated in an oven for one hour at 150°C. S.M. was then autoclaved in these cotton stoppered flasks at 120°C. for twenty minutes. After planting the bacilli, the cotton stoppers were replaced by aluminum foil or pyrex glass caps and inhibition of growth resulted. In the above experiment no paraffin was used at anytime. There was also inhibition if clean filter papers impregnated with paraffin wax of 53 to 55°C. melting point were used in place of the foil and glass caps of the above experiment. But if the acid-cleaned flasks were not stoppered with cotton at any time, there was no growth inhibition when filter paper sealed with paraffin, foil or glass caps were used as covers after planting of bacilli. The vapor and bubble tests referred to before demonstrated the presence of quite dense, previously invisible organic films, adsorbed by the inner glass walls when the cotton stoppers were heated in the oven with the flasks. This film could have been produced only by the distillates from the cotton. In the absence of cotton there was no such film. As might be expected, the amount of growth inhibition was not constant, ranging in amounts preventing growth from 10^{-3} to 10^{-7} mg. of the H37 strain and was more pronounced previous to the time when especial attention was given to cleaning the flasks.

Cohn (1944) confirmed the growth inhibition when cotton stoppers impregnated with paraffin were used; in one out of 3 flasks there was no growth from 10^{-4} mg. and in 2 out of 3 there was no growth from 10^{-6} mg. of the same strain of H37 of bacilli as used by the writer. The growth in 3 of the 6 flasks planted was delayed and less as compared with the flasks in which cotton stoppers were not used and in all of which there was growth. Cohn concluded, however, that

it was the paraffin and not the cotton distillates that was responsible, calling attention to the creeping tendencies of paraffin and the probable resulting retarded air or oxygen exchange between the S.M. and atmosphere. My own experiments using paraffin to *thoroughly* impregnate filter paper caps and seal them to the necks of flasks resulted in no inhibition of growth from the smallest numbers of planted bacilli. The placing of a few drops of mineral oil on the medium also permits growth from the smallest plantings. Furthermore, small lumps of paraffin, with melting points of 53° and 68°C., floated on the S.M. allowed growth from 10^{-7} and 10^{-8} mg. plantings, the same as for the controls.

The method of cleaning need not be that described above but it must be effective. The sodium salts of myristic and palmitic acids at 10^{-4} per cent concentrations inhibited the growth of 10^{-3} mg. (about 10^6 bacilli) of the H37 strain (Drea, 1944). The adsorption of molecular organic films by glass surfaces is a well established phenomenon. The sodium metasilicate and phosphate solution cannot introduce aliphatic compounds into the glassware and this is one of the principal reasons for its use.

Braun (1939) advised washing the flasks with soap-water and rinsing for a long time with tap water. The flasks are then filled with double distilled water and autoclaved for two hours, as he stated, to get rid of soluble substances in the glass walls. The flasks are then emptied, dried, stoppered with fat-free cotton and sterilized for two hours in the oven at 160°C. It is interesting to note that he specified *fat-free* cotton stoppers as this reduces the varieties of possible distillates. After planting the bacilli, the stoppers are sealed with paraffin of melting point 68 to 70°C.

Braun also stated that a standard of purity must be maintained in the incubator in order to prevent the admission of impurities from there into the culture medium. He remarked that the incubator may contain an important source of error, many microörganisms, including tubercle bacilli, being able to assimilate impurities from gaseous nitrogenous substances and carbonaceous nuclei. It is quite possible that at least some of the trouble attributed to the incubator by Braun is due to the charring, etc., of cotton stoppers, even when fat-free. The use of inert material for capping or plugging culture flasks eliminates the last mentioned risk. It has not as yet appeared necessary to take any other precautions in my work.

The amount of depth growth is variable depending upon the numbers of bacilli planted, the strain, the presence or absence of subsequent surface growth, incubation time and presence or absence of antibacterial substances. It ranges from that which is hardly visible to that of a considerably greater amount in comparison. It can be arbitrarily graded as + for one to 10 clumps, ++ for 10 to 25 clumps, +++ for 25 to 100 clumps and ++++ for a greater number of clumps. More scattered growth equivalent by estimate to the numbers of clumps mentioned may be similarly graded. At the end of two to three months' incubation there may be present in 20 ml. of S.M. 20 mg. of depth culture, weighed after excess moisture has been removed, but before it has been dried.

Cohn (1944) observed no difference between routinely cleaned culture bottles

capped by a thin layer of cork in a screw cap and the same bottles especially cleaned, being able to secure depth growth in each from 10^{-6} mg. plantings of the same strain of H37 bacilli used by the writer. These culture bottles had been repeatedly used for growing cultures of bacilli. Either his routine method of cleaning is effective or no antibacterial substances were present. But Cohn confirmed the findings for inhibitory effects when cotton stoppers impregnated with paraffin were used, concluding that the paraffin was responsible and not the cotton. The present writer believes he has demonstrated that it was the distillates from the cotton and not the paraffin that prevented growth of small numbers of bacilli.

No evidence was secured that pyrogenic substances were responsible for growth inhibition of the H37 strain. Seibert (1923) called attention to their presence in some distilled waters and demonstrated that they were relatively thermostable. Thermogenic substances also illustrate the importance of *clean* glassware. Welch *et al.* (1945) found pyrogens present on the inner walls of supposedly clean glass ampules. They reported that the thermogenic films may or may not be removed by the usual washing procedures and that they are not destroyed in the autoclave at 120° or at 160 to 170°C. in the dry oven. The readily adsorbed pyrogen was reported by them to be destroyed at 250°C. for forty minutes in the muffle furnace. The writer, in his earliest efforts to rid the culture flasks of the then suspected growth inhibiting organic films, relied on heating the flasks to incandescence. The fired flasks allowed the smallest numbers of bacilli to grow provided cotton stoppers were not used later. Strains were introduced into the glass as a result of the high temperature and uncontrolled cooling. Spontaneous breakage of some of the flasks occurred even days after they had been placed in the incubator and this method of making the flasks growth-permitting was given up.

SUMMARY

Submerged or depth growth will take place in Long's liquid synthetic culture medium when amounts as small as 10^{-7} to 10^{-8} mg. of H37 bacilli are planted.

If proper standards of cleaning the glassware are not maintained, growth may be limited to some amount of bacilli greater than 10^{-7} to 10^{-8} mg. Almost without exception, 10^{-2} mg. of the bacilli will grow even if the glass is not thoroughly cleaned.

One good method of cleaning glassware is described.

Distillates from nonabsorbent cotton stoppers were growth inhibiting and this became increasingly evident because of cumulative adsorption if the culture flasks were not thoroughly cleaned between growth periods.

Paraffin, of either 54°C. or 68°C. melting point, is not inhibiting to the depth growth of the smallest numbers of H37 bacilli.

SUMARIO

Sembrando hasta cantidades que no pasen de 10^{-7} a 10^{-8} mg. de bacilos H37, se formarán colonias sumergidas o profundas en el medio de cultivo sintético líquido de Long.

Si no se limpia la cristalería como procede, las colonias pueden limitarse a una cantidad de bacilos mayor de 10^{-7} a 10^{-8} mg., y casi sin excepción proliferarán 10^{-2} mg. de bacilos aunque no esté bien limpia la cristalería.

Descríbese aquí una buena técnica para la limpieza de la cristalería.

Los destilados de tapones de algodón inabsorbente inhibieron el desarrollo bacillar, lo cual se puso cada vez más de manifiesto debido a absorción acumulativa si no se limpiaban perfectamente los balones de cultivo entre los períodos de siembra.

La parafina de un punto de fusión, ya de 54°C. o 68°C., no inhibe las colonias profundas de las cantidades más pequeñas de bacilos H37.

BIBLIOGRAPHY

Berg, W. N.: The law of small numbers as applied to virulence measurement, Am. Rev. Tuberc., 1941, *43*, 685.

Braun, H.: Handbuch der biologischen Arbeitsmethoden, Abt. XII, Teil 2, I, 1–78, Urban & Schwarzenberg, Berlin-Wien, 1939.

Cohn, M. L.: Growth of human tubercle bacilli under restricted air conditions, Am. Rev. Tuberc., 1944, *49*, 463.

Corper, H. J., and Cohn, M. L.: The nutrient quality of eggs for growing tubercle bacilli, Am. J. Hyg., 1933, *18*, 1.

Drea, W. F.: The growth of human tubercle bacilli, H37, in synthetic medium with and without agar, J. Bact., 1940, *39*, 197.

Drea, W. F.: Growth of small numbers of tubercle bacilli, H37, in Long's liquid synthetic medium and some interfering factors, J. Bact., 1942, *44*, 149.

Drea, W. F.: Antibacterial effects of various organic substances upon the H37 strain of tubercle bacilli in a simple synthetic medium, J. Bact., 1944, *48*, 547.

Fildes, P.: A System of Bacteriology, 1931, *9*, 174–176, His Majesty's Stationary Office, London.

Gaddis, S.: An alkaline cleaning solution, J. Chem. Ed., 1942, *20*, 281.

Gaddis, S., and Kubina, K.: Distilled water supply for small schools, J. Chem. Ed., 1943, *20*, 381.

Laug, E. P.: Retention of bichromate by glassware after exposure to potassium bichromate cleaning solution, Indust. & Engin. Chem. (An. Ed.), 1934, *6*, 111.

Long, E. R., and Seibert, F. B.: A nonprotein medium suitable for the production of tuberculin in large quantity, Am. Rev. Tuberc., 1926, *13*, 393.

Richards, O. W.: Killing organisms as from incompletely washed bichromate—sulphuric acid cleaned glassware, Physiol. Zoöl., 1935, *9*, 246.

Seibert, F. B.: Fever producing substances found in some distilled waters, Am. J. Physiol., 1923, *67*, 90.

Tobie, W. C.: Nitric and sulphuric acids, a colorless cleaning mixture for glassware, J. Lab. & Clin. Med., 1941, *26*, 1797.

Welch, H., Price, C. W., Chandler, V. L., and Hunter, A. C.: The thermostability of pyrogens and their removal from penicillin, J. Am. Pharm. A. (Scient. Ed., 1945), *34*, 114.

DEPTH GROWTH OF ACID-FAST BACILLI IN LIQUID MEDIA[1]

II. Study of Various Technical and Theoretical Aspects

W. F. DREA

The technique described in paper I should result in 100 per cent of 10^{-7} mg. and about 50 per cent 10^{-8} mg. plantings of the H37 strain of human tubercle bacilli, producing depth growth when incubated at 37°C. in the liquid synthetic culture medium of Long and Seibert (1926), to be referred to as S.M. in the text. The following is a study of various technical and theoretical aspects of such growth.

EFFECT OF SEVERAL DIFFERENT WATERS IN THE S.M.

The following kinds of water were used in making the medium: sterile fractionally distilled water free from pyrogens (Abbott Laboratories), Colorado Springs drinking water as it came from the tap, the latter water evaporated to one-tenth of its volume and the same drinking water once and twice distilled. The distilled waters were used before and after they had opportunities of developing pyrogens. All of these permitted growth of the H37 strain from 10^{-7} to 10^{-8} mg. plantings. A spectrographic analysis of the drinking water had previously demonstrated the presence of the following elements in "traces": Al, Ba, B, Cr, Cu, F, Fe, Pb, Mn, Mo, Si, Ag, Sr, Ti and V (Drea, 1935).

Weight of depth growth in S.M.: The mass of bottom growth was determined only from those flasks which had no surface growth in addition. Distilled water was slowly poured into the flasks until the latter were almost filled. After the scattered culture had settled more water was added until a few ml. had gently flowed over the brim. The contents were then filtered through Eaton-Dikeman #850 filter paper, which is lintless, tight and hard. Four additional washings of the flasks were made with 5 ml. of distilled water to insure the removal of all the culture, each wash water passing through the filter before the next was added. In this way, any mineral oil added to prevent surface growth and gross amounts of dissolved substances in the culture medium were removed.

After nearly all of the final wash water had passed through the filter paper, the latter, with the bacilli on it, was removed from the funnel and placed on absorbent paper to remove most of the remaining liquid. The culture was then scraped off from the paper with the fire-smoothed end of a microscope glass slide and transferred to a tared watch glass which was placed in a dry incubator at 37°C. for twenty-four hours. It will be noted that the bacilli were not sterilized before weighing and that precautions must be taken to prevent contamination of the laboratory by the live bacilli. It also seemed desirable not to dry the bacilli at approximately 100°C., the usual procedure for getting rid of moisture.

The results of one experiment are recorded in table 1. Two drops of mineral

[1] From the Laboratory of the Colorado Foundation for Research in Tuberculosis at Colorado College, Colorado Springs, Colorado.

oil (Nujol) had been added after all of the 10^{-3} mg. and after some of the 10^{-6} mg. plantings in order to prevent surface growth.

The plantings of the H37 bacilli were made in 20 ml. of S.M. contained in 50 ml. Erlenmeyer pyrex flasks, the tops of which were closed by tightly wrapped aluminum foil which was not sealed to the glass. Each weight recorded is the average of 5 cultures.

A transplant from a seventeen month old culture to fresh S.M. resulted in good growth.

The amount of surface growth after thirty-four days' incubation when the cultures appeared to be at their maximum, following surface plantings on the

TABLE 1

Weight of depth cultures of H37 in 20 ml. of Long's medium. Cultures washed with distilled water and dried at 37°C. for twenty-four hours

INCUBATION TIME	AMOUNT OF BACILLI PLANTED	OIL OR NO OIL ON SURFACE OF S.M.	AVERAGE WEIGHT OF CULTURE
months	*mg.*		*mg.*
2	10^{-3}	Oil	5.06
	10^{-6}	Oil	2.18
	10^{-6}	No oil	2.92
4	10^{-3}	Oil	12.4
	10^{-6}	Oil	5.36
	10^{-6}	No oil	7.82
6	10^{-3}	Oil	19.5
	10^{-6}	Oil	14.5
	10^{-6}	No oil	19.26
9	10^{-6}	No oil	24.4
12	10^{-6}	No oil	25.8
17	10^{-6}	No oil	28.8

same amount of S. M. in similar flasks after treating and drying in the same way as for the depth growths, gave an average of 276 mg. for 6 cultures.

The small amount of mineral oil on the surface of the S.M. permitted increase of growth up to six months, the time limit of the oil film studies. The oil film cultures, however, were smaller from the 10^{-6} mg. plantings than from the same amounts of bacilli planted without an overlying oil film, possibly because the oxygen exchange between the atmosphere and the depth of the culture medium was obstructed by the oil or by probable reaction products of the oil and substances, metabolic or otherwise, in the culture medium. It is quite probable, also, that heating the oil to sterilize it may make it less growth-permitting, as there are some indications in this work that the same oil, not heated, will permit prompter growth.

The 10^{-3} mg. plantings at the end of two and four months' incubation produced only 2.3 times as much growth as the 10^{-6} mg. plantings, both being similarly covered with thin oil films, although the 10^{-3} mg. planting represented about one thousand times as many bacilli present. At the end of six months, the 10^{-6} mg. plantings with the overlying oil film showed growth approximating that of the 10^{-3} mg. plantings.

The 10^{-6} mg. plantings with no overlying oil films showed continuity of growth up to twelve months and probably up to seventeen months when the bacilli were viable.

A separate experiment where depth and surface plantings were made in each flask at the same time resulted in smaller amounts of depth growth than occur when there is no surface growth present. It is also a matter of observation that bottom growths do not appear to increase after development of spontaneous surface growths, which always occur with greater than 10^{-6} mg. submerged plantings of H37 bacilli. The failure of molecular oxygen to diffuse from the atmosphere into the medium because of the intervening surface growths and the metabolic products from the faster growing surface bacilli are offered as explanations for the lessened depth growths.

The preliminary report by Drea (1942) of 21 mg. for depth culture and 960 mg. for surface growth was for moist bacilli. The depth cultures had been growing for less than four months.

VIRULENCE TESTS WITH DEPTH CULTURES OF H37 BACILLI

The H37 strain had been growing submerged for a long time. This was done by planting, overlaying the S.M. with 2 drops of sterile mineral oil and incubating at 37°C.

On an average, transplants were made every thirty-four days for thirteen times. The thirteenth transplant was incubated for seventy-four days when suspensions of 10^{-4}, 10^{-6} and 10^{-7} mg. per ml. of 0.8 per cent sodium chloride in water were prepared. Subcutaneous injections of 1 ml. from each of these suspensions were made into 4 guinea pigs. The three groups (12 animals) were kept until they died. The autopsies showed extensive tuberculosis in all of the animals. The average duration of life for the 10^{-4} mg. was 104 days, for the 10^{-6} mg., 253 days and for the 10^{-7} mg. injections, 263 days.

A check for both asepsis and ability of the bacilli of the above experiment to reproduce themselves was made by planting 1 ml. each of 10^{-6} mg./ml. and 10^{-7} mg./ml. suspensions from each autoclaved hypodermic syringe previous to injecting the same amount into a guinea pig. A separate syringe was used for each animal and 4 flasks of S.M. were planted from each syringe. There was no contamination by other organisms and submerged growth resulted in all flasks. In addition, 0.1 ml. (measured by Pasteur pipette) of the 10^{-7} mg./ml. suspension was planted in each of 10 flasks of S.M. The estimated 10^{-8} mg. plantings produced growth in 8 of the 10 flasks.

Virulence tests for the same strain of bacilli grown only on the surface of the S.M. with similar groups of guinea pigs gave average survival times of 148 days

for the 10^{-4} mg., 254 days for the 10^{-6} mg. and 234 days for the 10^{-7} mg. injections.

It appears, then, that the H37 strain grown submerged for 482 days, during which 13 transplants were made, was as virulent for guinea pigs as is the same strain grown on the surface of the S.M. Also the ability of the submerged bacilli to reproduce themselves from very small numbers of bacilli is at least as great as that of surface growth bacilli.

The depth growth of these bacilli has been continued for 722 additional days, transplants having been made at average intervals of 103 days. They are now growing in the depth of the S.M. 1,204 days after the first planting.

Another viability test of the H37 strain after continuous submersion in the S.M. at 37°C. for six months, overlaid with 2 drops of mineral oil to prevent surface growth, resulted in 10^{-7} and 10^{-8} mg. plantings producing growth.

THE KAHN "SINGLE CELL" H37 STRAIN

This strain was developed from a single organism isolated from the H37 strain by Kahn (1929). According to Loebel, Shorr and Richardson (1933) the H37 strain was started about 1913 at the Trudeau Laboratory.

It seemed desirable to compare its growth properties with those of the H37 strain in our laboratory.

According to Dr. M. C. Kahn, in a personal communication, it had been growing in his laboratory on Long's synthetic medium. He transplanted it to a slant of Corper's egg medium and, when growth was well established, sent it to the writer. After its arrival it was transplanted and retransplanted several times to S.M. before depth growth tests were made, in order not to carry over biochemical substances from the egg-yolks.

It produced the same growth responses as does our H37 strain when planted in the depth of S.M. and on the surface of the S.M. In one experiment, 10^{-9} mg. of the Kahn culture produced growth in the S.M., as occasionally happened when the H37 strain was planted.

OTHER STRAINS OF ACID-FAST BACILLI

Two avian (Av. 6 and Av. 36), one bovine (Bov. Vir.), 2 smegma (Sewell and American Type Culture # 101), and one human (D) were grown in S.M. The findings are recorded in table 2, together with those for H37 and the Kahn "single cell" culture.

The human strain (D) and the bovine strain required relatively large plantings before depth growth occurred. The bovine strain was secured from Dr. M. L. Cohn who considers it to be glycerophylic (personal communication).

The 2 avian and 2 smegma strains produced depth growth from about as small amounts of bacilli as did the H37 strain.

DILUTION OF S.M. WITH WATER

The H37 and human D strains grew in the depth of S.M. diluted to 5 per cent with water. There was some indication, though the experiments are too few to

draw final conclusions, that certain diluted solutions of S.M. are more favorable during limited time periods of incubation for depth growth than is the full strength of S.M. The S.M. of full strength was originally planned to give an abundant amount of surface growth.

EFFECT OF MINERAL OIL ON DEPTH CULTURES IN S.M.

When one drop to 1.5 ml. of nonheated mineral oil was floated on the S.M. after planting 10^{-2} mg. of H37 bacilli, depth growth resulted.

TABLE 2

Smallest amounts of bacilli producing depth growth in 20 ml. of Long's medium

STRAIN	MG. PLANTED
Av. 6	10^{-8}
Av. 36	10^{-7}
Bov. Vir.	10^{-5}
Human (D)	10^{-4} occasional 10^{-5}
Smegma (Sewell)	10^{-8}
Smegma #101	10^{-7}
H37	10^{-7} to 10^{-8} occasional 10^{-9}
Kahn "Single Cell" H37	10^{-7} to 10^{-8} occasional 10^{-9}

DISCUSSION

It has been known for some time that tubercle bacilli will grow in the depths of various complex nonsynthetic liquid culture media.

Calmette (1928) referred to investigations by Besredka in 1913 and 1914 on depth growth in liquid media of meat bouillon and egg (the white and yolk). He also called attention to a simpler liquid medium used by Besredka in 1921 for the same purpose and composed only of egg-yolk in distilled water with sufficient Na_2CO_3 added to make it frankly alkaline to litmus. Calmette also reported on depth growths secured by E. Buc in 1924 directly from serous fluids such as pleural exudate and from tuberculous tissues. Kirchner (1931) called attention to the importance of depth growth studies in liquid culture media.

Novy and Soule (1925) stated that the essential reason for the organism not growing in the deeper layers of broth or agar media is the lack of oxygen and that, when the oxygen concentration in the atmosphere is increased to 80 or 100 per cent, there is a corresponding increase in the amount of oxygen dissolved by the broth or agar which then permits growth in the depth.

Boissevain (1931) concluded that tubercle bacilli grew through Long's medium containing suspensions of kephalin or lecithin. Evans and Hanks (1939) obtained depth growth from small numbers of the bacilli in liquid substrates of serum-leucocyte mixtures, blood or serum diluted with water or with Long's medium, in polymorphonuclear leucocytes and saline and in the washed cellular fraction of blood suspended in saline or dilute Long's medium.

The growth of the H37 bacilli in the depth of S.M. without added substances was demonstrated by Drea, who reported in 1940 that amounts "at least as small as 10^{-6} mg." and in 1942 that amounts at least as small as 10^{-7} to 10^{-8} mg. would grow. Boissevain (1943) confirmed these findings for as little as 10^{-8} mg. tubercle bacilli and recorded that, when no viable bacilli could be demonstrated, their absence was confirmed by guinea pig inoculation. Crimm and Martos (1944) reported that 4 out of 4 of 10^{-7} mg. and one out of 4 of 10^{-8} mg. plantings of H37 bacilli produced depth growth in S.M. Cohn (1944) obtained a culture of the H37 strain used by the present writer and secured depth growth in S.M. from 10^{-6} mg., apparently not planting smaller amounts.

The tubercle bacillus is generally considered to be an aerobe. Some strains such as the H37 when planted on the surface of S.M. and exposed directly to the oxygen of the atmosphere produce considerable growth on the surface. They can, however, survive, retain their virulence and grow when the supply of oxygen is much restricted.

Webb, Ryder and Gilbert (1918, 1921, 1923) concluded that the bacilli within tuberculous lymph nodes or pieces of liver and spleen removed from tuberculous guinea pigs and promptly replanted under the skin of normal guinea pigs invariably produced a general tuberculosis, which differed in no apparent way from that which follows inoculation with free virulent bacilli; that the most probable explanation for emulsified tubercle bacilli from cultures being able to survive and retain their virulence in normal salt solution at 37°C. for many days was because they were able to get a minimum of oxygen, whereas the bacilli within excised tuberculous tissues immersed in salt solution at 37°C. lost their virulence and probably died within a relatively few days because they were deprived of oxygen by the slowly dying tissues. There was not this rather rapid loss of virulence if the tisssues were kept at ice-box temperature. They were inclined to believe that, when tubercle bacilli survive and remain virulent for a long time in supposedly healed lesions, they are not completely encapsulated and there is still some biological exchange between them and the host's tissues because the bacilli die so quickly within incubated excised tuberculous tissues.

Webb, Boissevain and Ryder (1924), continuing the above investigations, placed tubes of normal salt solutions containing suspensions of tubercle bacilli from cultures in anaerobic jars. They concluded that the bacilli, when the tubes were incubated, lost their virulence at about the same rate as they do when enclosed within incubated tuberculous tissues, but retained their virulence when the tubes were kept at ice-box temperature.

Buc (1924) concluded that growth of tubercle bacilli is not possible in the depth of a nonsynthetic culture medium when the culture flask is evacuated and sealed.

Novy and Soule (1925), using a closed system and heavy plantings of H37 bacilli on surfaces of meat-extract-glycerol-agar media, recorded the growth of the cultures as proportional to the oxygen tension within certain limits. At 100 per cent volume oxygen there was less growth than at 40 to 50 per cent, which was the best tension for optimum growth. Below 40 per cent, the growth lessened proportionately as the oxygen tension was diminished, until at 0.5 per cent there was scanty growth. In one experiment with 0.19 per cent volume of oxygen, there was no growth indicated at the end of four weeks, though the bacilli were then viable as was shown by good growth one week later after the cultures were exposed to the atmosphere.

Corper, Lurie and Uyei (1927), using an open system with flowing gases and relatively heavy plantings of tubercle bacilli on surfaces of glycerol-agar media, confirmed the findings of Novy and Soule for oxygen tensions between that of atmospheric air at 628 mm. Hg and 0.1 per cent volume oxygen. At 0.5 per cent volume there was scanty growth. With 0.1 per cent there was no growth at the end of six weeks. When the 4 strains tested with 0.1 per cent volume of oxygen were then exposed for five weeks to atmospheric air, 3 of them produced growth.

Tubercle bacilli grow at the bottom of liquid S.M. in this laboratory where the average atmospheric pressure is 610 mm. Hg. The oxygen concentration available for the bacilli must be very low as distilled water at 37°C. and the same atmospheric pressure by calculation contains 0.387 per cent volume. Water with dissolved substances (such as S.M.) will probably contain less dissolved oxygen. With well established bottom growth and development of metabolic products, the amount of available oxygen may be further decreased. Growth of the submerged bacilli, where the S.M. was exposed to the atmosphere pressure, was demonstrated as increasing for more than twelve months. If 0.1 and 0.19 per cent volumes of oxygen, reported as not permitting the growth of heavy plantings on the surfaces of solid media, do not permit growth of submerged plantings in S.M. *containing the same concentrations of dissolved oxygen*, the range of oxygen concentrations not permitting, and permitting, growth must lie somewhere between the above figures and 0.387 per cent volume.

However, only experiment can determine that 0.1 or 0.19 per cent volume oxygen in the liquid S.M. will not permit depth growth.

Cohn (1944) has also called attention to the rôle of small amounts of air (oxygen) in the growth of tubercle bacilli and the difficulties of precise experimentation.

The application of Henry's law for the dissolving of atmospheric gases in liquids may simplify the problem. It applies to such liquids as water or plasma where oxygen would be in simple physical solution only and not to those liquids where there could be chemical combination between some constituent of the liquid and dissolved molecular oxygen. At 37°C. the amount of oxygen dissolved in distilled water is 0.025 times that in the atmosphere above. To insure 0.1 per cent volume of oxygen in the water it is only necessary to have 4 per cent volume in the atmosphere. It is probable that S.M. does not combine with dissolved oxygen. If full strength S.M. does not allow simple solution of oxygen, a sufficiently close approximation to this condition may probably be attained by

diluting the S.M. with water. H37 bacilli will grow at the bottom of a 5 or 10 per cent solution of S.M. Or some other medium that satisfies the requirements of Henry's law may be successfully used.

It would also appear that very small plantings of submerged bacilli offer a more precise means of experimentation. The growth from one-millionth of a mg. of H37 bacilli is visible in about twenty days and at the end of two months is about 10 million times that of the original planting, whereas with heavy plantings on the surfaces of solid media, the increase is relatively only a few fold and at the same time there is much greater total respiration and oxygen consumption.

Rigorous sealing of the necks of the 50 ml. Erlenmeyer culture flasks after planting the bacilli permitted readily recognized amounts of depth growth though less than when they were not sealed, if the incubation is continued for an indefinite time. The amount of atmospheric air available for the bacilli was less than 40 cc. The indication of complete sealing was the failure of the later spontaneous surface growths to go on to the usual profuse amounts customary with exposure to the atmosphere. Therefore, relatively small amounts of air, oxygen and other gases may be used for growth studies. Also, there can be no questioning of the occurrence of growth when the original plantings are invisible.

Loebel, Shorr and Richardson (1933), using the single cell strain culture isolated by Kahn *from the* H37 *strain, determined that the highest oxygen con*sumption in 3 ml. of the same Long's S.M. on the surface of which the bacilli had been growing was 2.7 c.mm./moist mg./hour measured in a Warburg apparatus at 37.5°C.

If the amount of oxygen consumption is the same for an actually growing submerged culture, there should be sufficient oxygen in a sealed 50 ml. flask containing 20 ml. S.M. to permit a visible amount of growth.

Actually, depth growth does result from 10^{-1} to 10^{-8} mg. plantings of H37 bacilli after the flasks are sealed at atmospheric pressure.

A 0.39 per cent volume of oxygen which permits depth growth is equivalent to 5.57×10^{-4} per cent grams or 5.57 p.p.m. and is to be considered a *trace* element under these conditions. The bacilli when planted on the surface of the S.M. are exposed to forty times this concentration of oxygen and the resulting culture in a nonsealed flask is much more profuse at its optimum than is a depth growth in a similar flask for the same time of incubation. It is to be noted, however, that the depth growth continues to increase for a considerably longer time after the surface growth has ceased. Because of the usual growth of the bacilli in tissues it would appear they may be more nearly "at home" when submerged in media than on the surface or on solid media such as glycerol-agar.

Buc (1924) reported that the bacilli of depth growth retained the same properties of acid-fastness and virulence as were characteristic of surface growth. The acid-fastness was confirmed by the present writer in 1940 and the virulence (this paper) for depth growth in S.M. Buc thought the depth growths with their continued retention of vitality, virulence and slower growth more nearly approximate the conditions of growth in animal tissues than do surface growths at me-

dium-atmosphere interfaces. The resemblances according to Buc are even more clear in direct cultures from such material as tuberculous pleural fluids, blood and tuberculous organs.

More evidence of the importance of limited supplies of oxygen is afforded by noting the apparent failure of established depth growth to increase after surface growth becomes established, as always occurs when 10^{-5} mg. or more of well dispersed H37 bacilli are planted in the S.M. Buc also noted this in his work. Planting on the surface of the S.M. immediately after making a depth planting greatly limits the depth growth. Overlying mineral oil films permit depth growth in S.M. from the smallest plantings that will grow in their absence. Buc used "oil of vaseline" to cover his more complex medium and obtained depth growth even when the medium with the overlying oil was heated to 100°C. in a water bath to drive the dissolved gases out of the medium previous to planting, offering the acceptable explanation that air must have diffused later into the culture medium through the oil.

The Kahn single cell H37 strain produced the same depth growth results as did the H37 strain in our laboratory. Kahn (1929) studied the growth resulting from single cells in microdroplets of the same S.M. My own studies by diluting the planting suspensions until vanishing small numbers of bacilli per ml. were present very probably resulted in single bacilli growing in much larger amounts of S.M.

In addition to the H37 and the Kahn "single cell" strains, 2 avian, one bovine and one human (D) strain grew when submerged in S.M. Youmans (1944) secured depth growth in a synthetic medium from heavy plantings of 5 virulent human strains, including the H37 RV strain, and from one avirulent strain. It appears to be probable that depth growth in synthetic media may be secured from all strains of acid-fast bacilli that will grow on the surface of the same medium, provided substances combining with dissolved oxygen are not present. Long's containing asparagin, the Long-Weinzirl with ammonium malate substituted for the asparagin of Long's medium, Crimm's (1944) with a hydrolysate of casein substituted for the asparagin and ammonium citrate of Long's medium and Youman's (1944) have been successfully used.

SUMMARY

Tubercle and smegma bacilli grow at the bottom of liquid synthetic culture media where the dissolved oxygen is present in only a few parts per million.

The amount of depth growth following the planting of 10^{-6} mg. of H37 bacilli in 20 ml. of Long's liquid synthetic medium increased for at least twelve months. At the end of seventeen months' incubation it averaged 28.8 mg. for 5 cultures, after washing and drying at 37°C. The amount of similarly treated maximum surface growth on the same amount of the medium averaged 276 mg.

The H37 bacilli were virulent for guinea pigs after 482 days of depth growth during which time they were transplanted thirteen times to the bottom of fresh synthetic medium. The injected bacilli had been growing submerged for seventy-

four days following the last transplant. Death from extensive tuberculosis resulted in 104, 253 and 263 days for an average of 4 animals each for 10^{-4}, 10^{-6} and 10^{-7} mg. bacilli, respectively.

It is probable that all strains of acid-fast bacilli will grow at the bottom of any liquid synthetic medium that will support surface growth, provided no substances combining with dissolved oxygen are present. Submerged growth of tubercle bacilli is more similar to growth in animal tissues than is surface growth.

Depth culture studies in liquid synthetic media offer an important means for investigating accessory growth factors. The same may be stated for at least part of the investigation of antibacterial substances.

SUMARIO

El bacilo tuberculoso y el del smegma proliferan en el fondo de medios sintéticos líquidos de cultivo, en los que el oxígeno disuelto sólo representa algunas partes por millón.

El número de colonias profundas consecutivas a la siembra de 10^{-6} mg. de bacilos H37 en 20 ml. del medio sintético líquido de Long, aumenta por lo menos durante 12 meses. A los 17 meses de incubación promedió 28.8 mg. en 5 cultivos después del lavado y la desecación a 37°C. La proporción máxima de colonias superficiales tratadas en forma semejante, promedió 276 mg. en la misma cantidad del medio.

Los bacilos H37 resultaron virulentos para cobayos al cabo de 482 días de cultivo profundo, durante cuyo tiempo fueron trasplantados trece veces distintas al fondo de un medio sintético reciente. Los bacilos inyectados habían sido cultivados en sumersión por 74 días después del último trasplante. La muerte debida a tuberculosis generalizada sobrevino en 104, 253 y 263 días en un promedio de 4 animales, cada uno con 10^{-4}, 10^{-6}, y 10^{-7} mg. de bacilos, respectivamente.

Es probable que todas las cepas ácidorresistentes crezcan en el fondo de cualquier medio sintético líquido que sostenga el desarrollo superficial con tal que no haya sustancias que se combinen con el oxígeno disuelto. Las colonias de bacilos tuberculosos sumergidas, son más semejantes que las superficiales a las de los tejidos animales.

Los estudios de los cultivos sumergidos en medios sintéticos líquidos, ofrecen un medio importante para estudiar los factores accesorios del desarrollo y lo mismo reza por lo menos en parte con la investigación de sustancias antibacterianas.

The author is grateful to Dr. M. L. Cohn, of the National Jewish Hospital, for the smegma (Sewell), avian and bovine cultures.

BIBLIOGRAPHY

Boissevain, C. H.: Some relations between immunity and biochemistry in tuberculosis, Am. Rev. Tuberc., 1931, *23*, 66.

Boissevain, C. H.: Survival of tubercle bacilli in solutions containing glycerol or its oxidation products, Proc. Soc. Exper. Biol. & Med., 1943, *54*, 342.

Buc, E.: Sur la croissance du bacille tuberculeux dans milieux liquides, Rev. de la tuberc., 1924, *5*, 520.

CALMETTE, A.: L'infection bacillaire et la tuberculose. Troisième édition, Masson et Cie, Paris, 1928.
COHN, M. L.: Growth of human tubercle bacilli under restricted air conditions, Am. Rev. Tuberc., 1944, *49*, 463.
COOPER, H. J., LURIE, M. B., AND UYEI, N.: The importance of the growth of tubercle bacilli as determined by gaseous tension, Am. Rev. Tuberc., 1927, *15*, 65.
CRIMM, P. D., AND MARTOS, V. F.: Effects of amigen and amino acids on the growth of tubercle bacilli, Am. Rev. Tuberc., 1944, *49*, 94.
DREA, W. F.: The spectrum analysis of hen eggs and chick tissues, J. Nutrition, 1935, *10*, 351.
DREA, W. F.: The growth of human tubercle bacilli, H37, in synthetic medium with and without agar, J. Bact., 1940, *39*, 197.
DREA, W. F.: Growth of small numbers of tubercle bacilli, H37, in Long's liquid synthetic medium and some interfering factors, J. Bact., 1942, *44*, 149.
EVANS, B., AND HANKS, J. H.: Growth of small numbers of acid-fast bacteria in blood and in serum, Proc. Soc. Exper. Biol. & Med., 1939, *40*, 112.
KAHN, M. C.: A developmental cycle of the tubercle bacillus as revealed by single-cell studies, Am. Rev. Tuberc., 1929, *20*, 150.
KIRCHNER, O.: Zur Veränderlichkeit des Tuberkuloseerregers in morphologischer Hinsicht, Beitr. z. Klin. d. Tuberk., 1931, *77*, 72.
LOEBEL, R. O., SHORR, E., AND RICHARDSON, H. B.: The influence of food stuffs upon the respiratory metabolism and growth of human tubercle bacilli, J. Bact., 1933, *26*, 139.
LONG, E. R., AND SEIBERT, F. B.: A non-protein medium suitable for the production of tuberculin in large quantity, Am. Rev. Tuberc., 1926, *13*, 393.
NOVY, F. G., AND SOULE, M. H.: Respiration of the tubercle bacillus, J. Infect. Dis., 1925, *36*, 168.
WEBB, G. B., RYDER, C. T., AND GILBERT, G. B.: An attempt to produce immunity by transplanting tuberculous lymph nodes into normal animals, Am. Rev. Tuberc., 1918, *1*, 693.
WEBB, G. B., RYDER, C. T., AND GILBERT, G. B.: The survival and virulence of tubercle bacilli in excised animal lymph nodes, Am. Rev. Tuberc., 1921, *5*, 388.
WEBB, G. B., RYDER, C. T., AND GILBERT, G. B.: Chronic experimental tuberculosis in the guinea pig, produced by transplanted tuberculous tissues, Tr. Nat. Tuberc. A., 1923, *19*, 290.
WEBB, G. B., BOISSEVAIN, C. H., AND RYDER, C. T.: Gas requirements of the tubercle bacillus, Am. Rev. Tuberc., 1924, *9*, 534.
YOUMANS, G. P.: Subsurface growth of virulent human tubercle bacilli in a synthetic medium, Proc. Soc. Exper. Biol. & Med., 1944, *57*, 122.

DIAMINODIPHENYLSULFONE DERIVATIVES

The Therapeutic Effects of Two New Derivatives in Experimental Tuberculosis

FRITZ T. CALLOMON[1] AND GEORGE W. RAIZISS[2]

The modern epoch of investigation on chemotherapy of experimental tuberculosis can be divided into two periods: the one extending over the years when sulfanilamide, sulfapyridine and certain related compounds were subjected to experimental tests in inoculated guinea pigs; the other marked by the use of 4,4′-diaminodiphenylsulfone and its derivatives. A pronounced superiority of the latter group of compounds over the sulfonamides previously used became evident (1 to 6). However, the parent drug, although the most effective of this group in deterring or restraining the development of experimental tuberculosis, proved also to be the most toxic. Conversely, its derivatives, such as promin, diasone and promizole, showed a much lower toxicity than did 4,4′-diaminodiphenylsulfone, and still a much higher curative effect in guinea pigs than did the sulfonamides of the earlier period. Their clinical trial in man, if carefully conducted by expert clinicians, seemed to be justified.

However, in the Editorial of the J. A. M. A. 1944, *125*, 149, it was emphasized that at present the use of these drugs in human therapy is "not without hazard," and that "the clinical reports as yet reviewed cannot justify any attitude concerning the value of these compounds in patients, than one of critical interest." Meanwhile, clinical and experimental investigation has been continued (7, 12) and has to be continued over long periods of time until a definite judgment will be possible whether or not certain sulfone compounds should be used for human therapy.

As a matter of fact, the search for new chemical compounds has been continued also, with the aim of increasing the curative effect and of diminishing the toxic properties of new chemical agents to be used against tuberculosis. In the following report we are concerned with another new sulfone product which, under the conditions of our experiments, was strikingly well tolerated when administered to guinea pigs over a long period of time, and which proved to be at least as effective in restraining or preventing the development of tuberculosis as diasone. This new product is compound No. 2412 of the Dermatological Research Laboratories (Division of the Abbott Laboratories, North Chicago, Illinois) in Philadelphia. Another sulfone product, that is, No. 3206, of the same laboratories has been included and the effectiveness of both new compounds was compared with diasone in our experiments.

THE THREE COMPOUNDS USED IN THIS STUDY

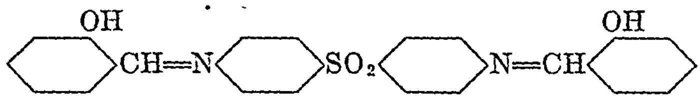
(a) *Diasone:* As to the chemical properties, the effectiveness and the toxicity of diasone, we refer to the literature (5, 6, 13), in particular to the recent detailed

[1] From The Research Institute of Cutaneous Medicine, Dr. John A. Kolmer, Director, Philadelphia, Pennsylvania.

[2] From the Dermatological Research Laboratories, Philadelphia, Pennsylvania (Division of Abbott Laboratories, Chicago, Illinois).

report of Raiziss, Severac and Moetsch (8). The low toxicity of diasone for mice, rats, rabbits and dogs has been determined by these authors. In addition, in connection with our present studies, the chronic toxicity of diasone for guinea pigs was also determined. Results will be presented in connection with those obtained with No. 2412.

(b) *The new products Nos. 2412 and 3206:* No. 2412—p,p′-di-(2 hydroxy benzal-amino) diphenylsulfone:

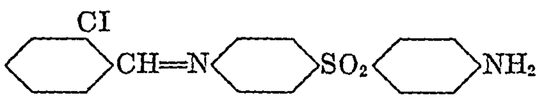


It is orange red crystalline material, insoluble in water, difficultly soluble in alcohol, somewhat soluble in acetone, soluble in warm benzol, insoluble in ether or petroleum ether.

This product is formed by reacting 2 moles of salicylaldehyde (2-hydroxy-benzaldehyde) with one mole of diaminodiphenylsulfone in methyl alcohol. Both amino groups of the diphenylsulfone are substituted.

This product is stable to oxidation. It is hydrolyzed by dilute hydrochloric acid, it can be diazotized and the amino groups quantitatively estimated by a colorimetric method. In this way it was determined that the product does not undergo a change when exposed to air. Diazotization value as determined by photoelectric colorimeter remains constant after a long exposure of the drug to air. No. 2412 does not become oxidized on exposure to air as does diasone.

No. 3206—p-(5 chlor 2 hydroxy benzal-amino) p′-amino-diphenylsulfone is insoluble in water, slightly soluble in alcohol, soluble in acetone.



(c) *Chronic toxicity of diasone and product No. 2412 for guinea pigs:* The following studies on chronic toxicity and blood concentrations were conducted in normal guinea pigs kept under the same conditions as the animals used for our tuberculosis experiments. The percentages of the drugs administered corresponded to the dosage used for the treatments of our inoculated guinea pigs.

In order to determine the chronic toxicity of diasone in guinea pigs, it was given in the food in a concentration of 0.6 per cent. Two groups of animals were maintained. Drug diet was fed to the first 5 pigs for six months and twenty-seven days. All animals survived. The weight of each animal increased over this period from an average weight of 460 g. to an average of 776 g. From the great increase in weight, one can conclude that these animals tolerated diasone very well indeed for a long period of time. A second group of 5 animals was given the same drug diet for a period of five months and four days. The average weight of these animals at the start of the experiment was 284 g. and at the end it was 804 g. This second experiment corroborated the findings of the first and the conclusion remains that the tolerance of the animals for diasone was high.

The chronic toxicity of compound No. 2412 proved also to be low. Two groups of animals were also maintained. Six guinea pigs weighing an average of 366 g.

on the first day of the experiment were fed a diet containing 0.5 per cent of compound No. 2412; they received this diet for a period of three months and sixteen days. At the conclusion of the experiment, the average weight of the animals was 718 g. The second group, consisting of 12 animals, was given the same drug diet for 105 subsequent days in accordance with the period of treatment used in our present tuberculosis studies. The pigs of both groups survived, increasing over this period from an average weight of 398 g. to an average weight of 652 g. From these results it could be seen that the chronic toxicity of product No. 2412 is very low and comparable in this respect to diasone.

At the end of these experiments autopsies of sacrificed animals were made and the spleens and livers of 3 animals fed with each compound submitted to microscopic examination. Generally, a slight to moderate enlargement and a bluish or dark blue color of the spleens was observed, while the microscopic examination revealed some vacuolization of peripheral liver cells in several lobules of the livers.

(d) *Blood level determinations in guinea pigs given drug diet containing diasone or No. 2412:* The blood levels in the first group of guinea pigs which received a drug diet containing 0.6 per cent diasone were determined on the seventy-sixth day of the experiment. For the 5 animals the blood levels averaged as follows: free diasone 0.75 mg., conjugated 0.16 mg., total 0.91 mg. Blood levels were taken again on the eighty-third day and the average was found to be: free diasone 1.59 mg., conjugated 0.27 mg., total 1.86 mg.

In the second group of 5 animals receiving a similar diet of 0.6 per cent diasone, the blood levels were taken on the sixth day of the experiment with the average of: free diasone 0.75 mg., conjugated 0.44 mg., total 1.19 mg. On the twenty-second day the average was: free diasone 1.18 mg., conjugated 0.25 mg., total 1.43 mg. The findings on the thirty-fourth day were: free diasone 1.47 mg., conjugated 0.65 mg., total 2.12 mg.

From the above it could be seen that the diasone blood levels in guinea pigs are uniformly low.

The blood levels in the first group of guinea pigs which received a diet containing 0.5 per cent of product No. 2412 were estimated after the animals were fed the above diet for six days. The results were: free drug 1.19 mg., conjugated 0.55 mg., total 1.74 mg. The next determination of blood levels was done after the guinea pigs continued this diet for twenty-five days. The findings were: free drug 0.84 mg., conjugated 0.15 mg., total 0.99 mg. The last determination was made after fifty-four consecutive days of the drug diet. The blood levels were: free drug 0.98 mg., conjugated 0.98 mg., total 1.96 mg. These figures indicate that, as with diasone, low blood levels were obtained throughout the entire period of administration of compound No. 2412.

EXPERIMENTAL CHEMOTHERAPY

One hundred and thirty-four guinea pigs weighing 300 to 400 g. were inoculated subcutaneously in the groin, using a fresh subculture of a human strain of tubercle bacilli, that is, strain H42133 of the Phipps Institute, Philadelphia. The dose

given to each animal was 0.0004 g. of tubercle bacilli per 100 g. of body weight. Twenty guinea pigs remained untreated serving as controls, 114 were submitted to treatment by drug diet. The animals were kept in individual cages. Two series were maintained, the one consisting of 60 guinea pigs put on drug diet three days after inoculation, the other consisting of 54 guinea pigs put on drug diet thirty days after inoculation. Both series were subdivided into three groups, each group corrsponding to one of the 3 compounds. The three groups of the first series consisted of 20 animals each; the three groups of the second series of 18 animals each. Drug diet was prepared by incorporating the various compounds into the food, which consisted of ground "rabbit chow;" 2 per cent corn syrup was added to make the drug diet as palatable as possible. The food, whether containing drug or consisting of pure "rabbit chow," was supplemented by small amounts of fresh vegetables.

Before drug diet was started all guinea pigs had been pre-fed with the basic food for one week, that is, until the food intake became constant. From the beginning of the second week an average intake of 35 to 40 g. per day per animal was noted. Another eight-day period of observation proved to be necessary in order to obtain a constant intake after drug had been added to the food.

Our experiment, therefore, was planned as follows:

Series I, put on drug diet three days after inoculation	Group 1 consisting of 20 animals given diasone Group 2 consisting of 20 animals given No. 2412 Group 3 consisting of 20 animals given No. 3206
Series II, put on drug diet thirty days after inoculation	Group 1 consisting of 18 animals given diasone Group 2 consisting of 18 animals given No. 2412 Group 3 consisting of 18 animals given No. 3206

During the first two weeks after inoculation all three compounds were given in an equal percentage with the food, that is, 0.66 per cent. However, the drug concentration had to be cut down in the course of the following two weeks when toxic symptoms became obvious (in some animals the appetite seemed to decrease and the autopsies of a few animals which died early revealed toxic changes in the spleens and livers, the spleens showing a characteristic dark blue color and slight enlargement). Thereafter, diasone was administered in a concentration of 0.6 per cent and compound No. 2412 in a concentration of 0.5 per cent with the food. The dosage of No. 3206 had to be cut down gradually to 0.3 per cent. From the thirtieth day after inoculation up to the end of the experiment these doses were well tolerated. According to an average intake of 35 to 40 gm. of drug food per day per animal, we estimated the daily drug intake to be as follows: 210 to 240 mg. of diasone, 175 to 200 mg. of No. 2412 and 105 to 120 mg. of No. 3206.

During the entire period of treatment, drug food was freshly prepared and continuously supplied by the Dermatological Research Laboratories (Division of the Abbott Laboratories, North Chicago, Illinois) in Philadelphia. The food containing No. 2412 or No. 3206 was supplied every week, while diasone diet was prepared twice a week because diasone proved to be somewhat oxidizable when kept in partly emptied bottles for more than a few days.

During the whole experiment the weights of all guinea pigs were recorded weekly. One hundred and three days *after inoculation all survivors were sacrificed*. At that time the survivors of series I had been treated with the various compounds of one hundred subsequent days and those of series II for seventy-three days.

Autopsies were made on all animals which died during treatment or were sacrificed at the end of the experiments. The degree, distribution and character of the tuberculous lesions were determined macroscopically and microscopically, by direct smear examination as well as by histological examination of spleens, livers, lungs and lymph nodes.

RESULTS

Survivors: At the end of our experiment, that is, 103 days after inoculation, only 7 (35 per cent) of the 20 untreated controls were alive. Deaths of the controls occurred between the 38th and 102nd days, except for one animal which died on the twenty-sixth day after inoculation. In this guinea pig autopsy revealed extensive pneumonia of both lungs; at that early time tuberculous lesions were already present in spleen and liver, and smears taken directly from the spleen showed tubercle bacilli.

Comparatively, 88 (77 per cent) of the 114 treated animals survived. However, the mortality observed with the various compounds differed markedly. Fifteen deaths were observed with compound No. 3206, while mortality was low with diasone (5 deaths) and No. 2412 (6 deaths). Thus, the mortality rates after treatment with diasone, No. 2412 and No. 3206 were: 13.2, 15.8 and 39.5 per cent, respectively, while that of the untreated controls amounted to 65 per cent. In this statement we included 3 early deaths, one animal of each compound, which died before the thirtieth day after inoculation. These cases will be discussed later on.

As to the survival times of the guinea pigs dying during the period of treatment, the deaths observed with diasone occurred between the thirty-third and ninety-eighth days, with No. 2412 between the fiftieth and seventy-seventh days and with No. 3206 between the thirty-fourth and ninety-eighth days after inoculation. There were no differences of any consequence in the mortalities of the two series, whether put on drug diet on the third day or on the thirtieth day after inoculation.

The numbers of survivors and deaths observed with the various groups and compounds are summarized in table 1.

Body weight: The records of body weights showed significant differences between treated and untreated guinea pigs, as well as among the various compound groups. From the eighth to ninth week most of the controls did not increase in weight; a progressive decrease became evident. Conversely, most of the surviving guinea pigs given diasone or No. 2412 increased in weight throughout treatment. After administration of No. 3206, however, only a few of the surviving animals showed a continuous increase, while the other guinea pigs showed slight increase alternating with periods of decrease or rapid loss in weight.

Pathological changes: To the summary of our results obtained by autopsies and microscopic investigation, we wish to eliminate the above mentioned 3 early deaths, one from each compound. These 3 animals died on the tenth, twelfth and fourteenth day after inoculation; moreover, there was evidence of toxic damage, the spleens showing enlargement and a dark blue color, generally indicating a toxic effect of sulfa-drug administration (9). We eliminated also another animal which died on the thirty-second day. This guinea pig had been put on No. 3206 diet just three days before death. The cause of this death remained questionable; evidence of toxic damage was not found at autopsy, nor were there any tuberculous lesions large enough to account for death.

Our histopathological findings proved to be largely concordant with the findings at autopsy. Our results are summarized in chart 1. The graphs demonstrate both the mortality rates and the degrees and distribution of tuberculosis

TABLE 1

GROUPS OF UNTREATED AND TREATED ANIMALS		NUMBER OF ANIMALS USED	SURVIVORS		DEATHS DURING TREATMENT	MORTALITY RATE
			Each group	Total		
Controls (untreated)		20	—	7	13	65
Diasone	Group I	20	16	33	4	13.2
	Group II	18	17		1	
No. 2412	Group I	20	16	32	4	15.8
	Group II	18	16		2	
No. 3206	Group I	20	12	23	8	39.5
	Group II	18	11		7	

in treated and untreated animals. The same scale of three degrees was used that we used in earlier studies on diasone and other compounds (5); degree I indicating a few discrete epithelioid tubercles in the spleens, livers or lungs; degree II a moderate number of tuberculous lesions showing a focal rather than diffuse development; degree III a wide-spread progressive and destructive tuberculosis.

As verified by autopsies and microscopic examinations, the treated animals showed not only fewer tuberculous lesions than did the untreated controls, but also a histological character of tuberculosis quite different from that of the tuberculosis found in the untreated animals. This contrast became most impressive when autopsies of the sacrificed survivors were made. However, there were also marked differences between the pigs given diasone or No. 2412 and those given No. 3206.

The animals treated with diasone or No. 2412, whether drug diet was started on the third or thirtieth day after inoculation, generally showed a slight or

moderate involvement. The slightest development (degree I) was noted in 19 pigs given diasone (51.4 per cent) and in 18 given No. 2412 (48.5 per cent). A moderate development (degree II) was noted in 15 guinea pigs given diasone (40.5 per cent) and in 17 given No. 2412 (46 per cent), while severe tuberculosis (degree III) was rare with these two compounds (3 animals of the diasone groups

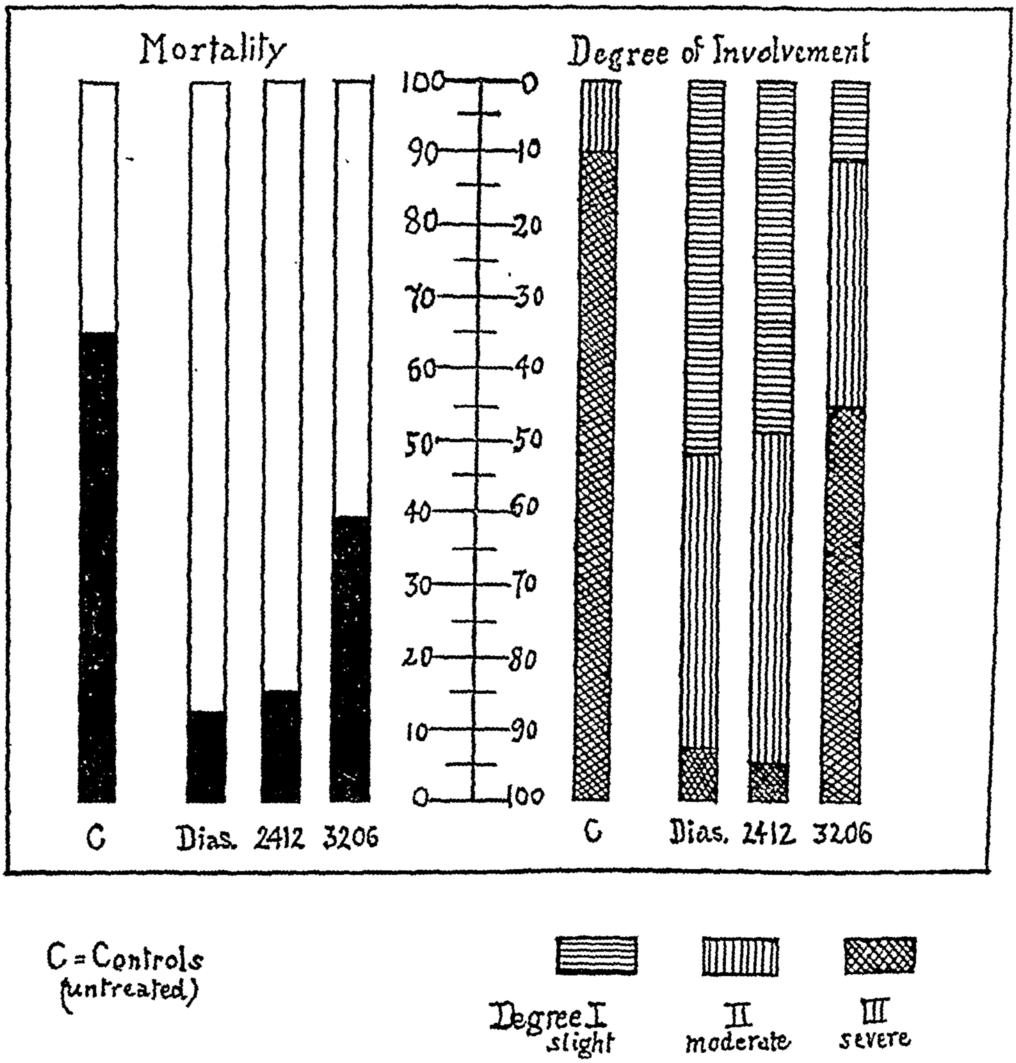


CHART 1. Mortality rates and degrees of involvement in treated and untreated animals

and 2 of the No. 2412 groups). In comparison, the animals of the No. 3206 groups showed a total of 20 severe cases (55.6 per cent) and 12 cases of a moderate involvement (33.3 per cent). Only in 4 animals of the No. 3206 group was a slight development noted comparable with the favorable findings after diasone or No. 2412 treatment. In this statement of percentages we did not include the above mentioned 3 cases of early deaths nor the one questionable case.

In all animals which showed degree I, the tuberculous nodules in the spleens and livers were scarce and small and frequently restricted to one of the two organs; microscopic examination revealed no further involvement. In these cases necrosis was always slight and not frequent. The lungs when afflicted, showed tuberculous lesions limited to relatively small areas without extensive necrosis. In the organs of sacrificed survivors given diasone or No. 2412 we also found retrogressive changes in the organs, as described and demonstrated by photomicrographs by Feldman and his associates (1, 4, 6) in their reports on the effects of certain sulfone compounds. Solitary tubercles were observed showing fibroplastic changes or changes of the epithelioid cells indicating a regressive phase of the tuberculous process. We also observed single tuberculous nodules surrounded by a dense wall of lymphocytes and also of histiocytes as described by Feldman (1, 4).

In contrast, the untreated controls, whether dying during or sacrificed after treatment, exhibited uniform evidence of an unrestrained progression of the tuberculous process, that is, a wide-spread dissemination with diffuse necrosis, with the exception of 2 guinea pigs. These 2 animals showed only a moderate involvement; the one, as mentioned, died of pneumonia twenty-six days after inoculation, the other, which survived, showed only a few tubercles in the lungs and spleen, but extensive necrotic areas in the severely involved liver.

DISCUSSION

As can be seen from the tabulated results of this study, the deterring or curative influence of certain derivatives of 4,4′-diaminodiphenylsulfone on experimental tuberculosis of guinea pigs again became evident. The prolonged administration of diasone as well as of No. 2412 reduced the mortality rates of the inoculated guinea pigs to a low percentage and restrained the progression of the morbid process. Our determinations of the chronic toxicities of both compounds for normal guinea pigs have shown that they are well tolerated in the dosage used. The new product No. 2412, although given in a somewhat smaller dosage than diasone, proved to be about equally effective. It is superior to diasone with regard to its stability to oxidation; for exposure to air does not influence its chemical and biological properties. Diasone, on the other hand, has to be protected from oxidation in vacuum ampules in order to remain stable (11). Our blood level studies, conducted during long periods of drug intake, showed an equally low level after diasone and No. 2412 administration.

The therapeutic superiority of diasone and No. 2412 over the other new product No. 3206 has been reflected by the mere fact that the mortality rate after treatment with the first two compounds was approximately one-fifth and one-fourth, respectively, of that of the untreated controls, and that a nonprogressive character of the pathological changes in the organs prevailed. On the other hand, the mortality rate after treatment with No. 3206 amounted to almost two-thirds of that observed with the controls. Only a minor part of the animals given No. 3206 showed a nonprogressive form of tuberculosis; a considerable number

exhibited severe pathological changes at autopsy comparable with those in the untreated controls. However, we feel that a great many of the deaths occurring after No. 3206 diet were due to the toxic influence of the higher dosage used during the first weeks of our experiment. After the dose had been cut down, the effect of drug was not sufficient to exert a beneficial effect comparable with diasone or No. 2412.

Our results obtained with diasone when given with the food have corroborated the favorable results which we observed in earlier experiments when 0.1 g. of diasone was administered by mouth twice a day (5). Our recent observations with diasone correspond also to those published in 1943 by Feldman and his associates (4) and recently by Corper and Cohn (12).[3]

Comparing the pathological changes in the animals of the compound groups which had been put on drug diet three days after inoculation with those put on drug diet thirty days after inoculation, we did not find differences of any consequence.

SUMMARY AND CONCLUSIONS

Two new compounds have been subjected to this experimental study; their effectiveness and toxicity were determined and compared with diasone. The one of the two new compounds was No. 2412, the other No. 3206 of the Dermatological Research Laboratories, Philadelphia (Division of the Abbott Laboratories, North Chicago, Illinois). The chemical structures and properties have been described.

We have interpreted the results obtained under the conditions of our experiments as indicating:

(*1*) A marked deterring effect on the development of tuberculosis of the new product No. 2412, which proved to be equal to diasone when given in a somewhat lower dosage for a similar period of treatment.

(*2*) A therapeutic effectiveness which proved to be the same whether drug diet was started three days or thirty days after inoculation.

(*3*) The superiority of No. 2412 and diasone over No. 3206.

(*4*) Product No. 2412 chemically is 2 hydroxy benzaldehyde, derivative of diaminodiphenylsulfone. It is superior to diasone in its stability to oxidation. Its chemical and biological properties are not affected on exposure to air.

(*5*) Experiments on the chronic toxicity of diasone for guinea pigs indicate that the toxicity is very low. This confirms the findings of Raiziss, Severac and Moetsch (8) for mice, rats, rabbits and dogs.

(*6*) The blood levels obtained with diasone in guinea pigs are comparatively low and on the order of those found for mice, rabbits and dogs (8).

(*7*) Product No. 2412, similar to diasone, exhibited low chronic toxicity for guinea pigs accompanied by low blood levels.

[3] The latter authors, however, believe that the retarding effect of diasone on tuberculosis in guinea pigs is due to the cyanotic effect on the internal organs (such as spleen and liver) rather than to any direct bactericidal or bacteriostatic action; that is, that a definite anoxemia produced by effective amounts of diasone is largely related to the effect noted (12).

(*8*) In our experiments, product No. 3206, although given in a lower dosage than No. 2412 and diasone, showed a greater toxicity.

(*9*) The inclusion of product No. 2412 with other sulfone compounds in further investigation appears justified.

SUMARIO Y CONCLUSIONES

Dos nuevos compuestos fueron objeto de este estudio experimental, determinándose su efectividad y toxicidad y comparándose con las de la diasona. Uno de los dos nuevos compuestos fué el No. 2412 y el otro el No. 3206, de los Dermatological Research Laboratories, Filadelfia (parte de los Abbott Laboratories, North Chicago, Illinois). Se han descrito la estructura química y propiedades.

La interpretación de los resultados obtenidos bajo las condiciones de los experimentos ejecutados indican:

(*1*) Decidido efecto adverso al desarrollo de la tuberculosis de parte del nuevo producto No. 2412, que resultó igual a la diasona, administrado en dosis algo menores, durante un período semejante.

(*2*) Eficacia terapéutica que resultó idéntica, ya se iniciara la medicación 3 ó 30 días después de la inoculación.

(*3*) Superioridad del No. 2412 y de la diasona sobre el No. 3206.

(*4*) El producto No. 2412 químicamente es 2 hidroxibenzaldehido, derivado de la diamino-difenil-sulfona, siendo superior a la diasona en su estabilidad a la oxidación, sin que la exposición al aire altere sus propiedades químicas y biológicas.

(*5*) Los experimentos relativos a la toxicidad crónica de la diasona para los cobayos indican que es bajísima, lo cual confirma los hallazgos de Raiziss, Severac y Moetsch (8), en ratones, ratas, conejos y perros.

(*6*) Las concentraciones sanguíneas obtenidas con la diasona en los cobayos son relativamente bajas y del mismo orden que las observadas en ratones, conejos y perros (8).

(*7*) El producto No. 2412, semejante a la diasona, manifiesta poca toxicidad crónica para los cobayos, acompañada de concentraciones bajas en la sangre.

(*8*) En estos experimentos, el producto No. 3206, aunque administrado a dosis más pequeñas que el No. 2412 y la diasona, reveló mayor toxicidad.

(*9*) Parece justificada la inclusión del producto No. 2412 con otros compuestos de la sulfona en las investigaciones ulteriores.

REFERENCES

(1). Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: The effects on experimental tuberculosis of 4,4′-diaminodiphenylsulfone, Am. J. M. Sc., 1944, *207*, 290.

(2). Smith, M. J., Emmart, E. W., and Westfal, B. B.: The action of certain sulfonamides, sulfones and related phosphorus compounds in experimental tuberculosis, J. Pharmacol. & Exper. Therap; 1942, *74*, 163.

(3) Emmart, E. W., and Smith, M. J.: The attenuating effect of promin on virulence of the tubercle bacillus, Proc. Soc. Exper. Biol. & Med., 1942, *51*, 320.

(4) Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: Therapeutic effect of disodium formaldehyde sulfoxylate diaminodiphenylsulfone in experimental tuberculosis, Arch. Path., 1943, *36*, 64.

(5) CALLOMON, F. F. T.: New derivatives of diaminodiphenylsulfone: their therapeutic effect in experimental tuberculosis of guinea pigs, Am. Rev. Tuberc., 1943, *47*, 97.
(6) FELDMAN, W. H., HINSHAW, H. C., AND MOSES, H. E.: Promin in experimental tuberculosis: Sodium p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate, Am. Rev. Tuberc., *1942*, *45*, *3030* and *1942*, *46*, *187*.
(7) FELDMAN, W. H., HINSHAW, H. C., AND MANN, F. C.: The effects on experimental tuberculosis of 4,2 diaminodiphenyl-5'-thiazolesulfone (promizole); and HINSHAW, H. C., FELDMAN, W. H., AND PFUETZE, K.: The clinical administration of promizole in tuberculosis, Proc. Staff Meet., Mayo Clin., 1944, *19*, 26 and 33.
(8) RAIZISS, G. W., SEVERAC, M., AND MOETSCH, J. C.: *Diasone, its toxicity and* therapeutic effectiveness, J. Lab. & Clin. Med., 1945, *30*, 317.
(9) CORPER, H. J., AND BOWER, C.: Sulfanilamide in tuberculosis, Am. Rev. Tuberc., 1939, *40*, 452.
(10) PETTER, C. K., AND PRENZLAU, W. S.: Treatment of tuberculosis with diasone, Am. Rev. Tuberc., 1944, *49*, 308.
(11) RAIZISS, G. W., CLEMENCE, L. W., AND FREIFELDER, M.: Synthesis and chemical properties of diasone, J. Am. Pharm. A. (Scient. Ed.) 1944, *33*, 43.
(12) CORPER, H. J., AND COHN, M. L.: The use of diasone for the treatment of tuberculosis, J. A. M. A., 1945, *127*, 1043.
(13) RAIZISS, GEORGE W. Diasone: A new and active chemotherapeutic agent, Science, 1943, *98*, 350.

EFFECT OF HUMAN GASTRIC JUICE ON TUBERCLE BACILLI[1]

With Special Reference to the Diagnosis of Active Pulmonary Tuberculosis

C. H. KRAMER[2]

The question of whether one is dealing with minimal active "open" tuberculosis or with a healed inactive lesion is one to which a prompt and decisive answer is often urgently desired. In such a case a discrepancy between two laboratory procedures, as between the results of guinea pig inoculation and the findings on a direct smear of gastric juice, is very disturbing to both physician and patient. Two case histories will illustrate the problem.

CASE HISTORIES

Case 1: V. N., a 20 year old white woman, entered the dispensary on December 16, 1943, in the seventh month of pregnancy. At this time she had no complaints other than loss of appetite. Physical examination revealed moist râles and increased *tactile fremitus* over both upper lung fields posteriorly. Her mother had died of tuberculosis when the patient was 2 years old, but no other tuberculous contacts were known. When she was examined by a medical consultant there were no longer any râles heard and the previous findings were attributed to a recent attack of "flu." Fluoroscopy and X-ray films made anteroposteriorly and laterally showed some fibrotic changes in both lower lobes, but no evidence of apical infiltration. On January 7, 1944 examination of a smear of the stomach contents revealed "a few typical and atypical acid-fast bacilli." Guinea pigs inoculated with the specimen at this time were autopsied two months later, but no evidence of tuberculosis could be found. No colonies of tubercle bacilli developed on culture. The patient completed her pregnancy before another lavage and inoculation could be done. Because of the questionable findings it was felt that the infant should be isolated from the mother until a definite diagnosis could be established. At the time of her discharge from the hospital this was still impossible.

Case 2: G. F., a 48 year old male Negro, dining car attendant, entered the dispensary on August 12, 1944, with intermittent attacks of dull chest pains, headache and dizziness, accompanied by nonproductive cough. The patient had had gonorrhea in 1936 and, six months previously, had been found to have a blood Wassermann reaction of 4-plus. Physical examination revealed increased tactile fremitus and vocal resonance with a few moist râles over both upper lung areas. Systolic murmurs were heard over the mitral and pulmonic areas. He had a sedimentation rate of 26 mm. per hour, no rise in daily temperature, 4-plus Wassermann and Kahn reactions. He occasionally coughed up flecks of blood. Fluoroscopy and X-ray diagnosis was bilateral fibrotic upper lobe tuberculosis *with cavitation and questionable activity. On November 22 many atypical and a few* typical acid-fast bacilli were found in the gastric washings. Inoculation of this specimen into guinea pigs failed to produce any evidence of tuberculosis in two months. Repeated sputum examinations were negative for acid-fast organisms. On March 21 another gastric washing showed several acid-fast bacilli per high power field. No evidence of tuber-

[1] First report written on a study made as a partial requirement for the degree of Master of Science in Medicine in the graduate school, University of Illinois, College of Medicine, Chicago, Illinois.

[2] Present address: 2917 West Jackson Blvd., Chicago, Illinois.

culosis could be found in guinea pigs inoculated with this specimen. No colonies of tubercle bacilli could be grown by culture methods. Because of the patient's position as a food handler in a railroad dining car, an exact evaluation of his ability to transmit a tuberculous infection was required. However, the activity of the lesions is not defined at present because of the equivocal laboratory findings.

In the past year (April 1, 1944 to April 1, 1945) 103 gastric lavages have been performed at the University of Illinois Research and Educational Hospital as an aid in the diagnosis of pulmonary tuberculosis. In 18 (17.7 per cent) of these lavages acid-fast bacilli, morphologically resembling tubercle bacilli, were found by microscopic examination, but no colonies could be grown from the washings and typical visceral tuberculosis could not be produced after inoculation into guinea pigs (1).

DISCUSSION

In the 2 cases reported it can be seen that a conclusive decision as to the presence or absence of active pulmonary tuberculosis would have been of great practical value. If a patient has active disease, he should be placed on adequate therapy for his own protection and for the safety of his family and associates. If there is no active lesion, however, he should be spared the waste of time, the expense and the worry of prolonged therapy. This report is concerned with the nature and identity of these acid-fast rods and their failure to grow in cultures or to infect guinea pigs. The problem has practical significance in a small, but none the less important, group of patients with regard to accurate diagnosis, early therapy as required, and reliable prognosis.

The organisms under investigation are probably not mere acid-fast saprophytes which have been introduced into the stomach with raw fruit, vegetables, tap water, air, or nasal secretions. The majority of such saprophytes produce characteristic, rapidly growing colonies on culture media and usually can be differentiated microscopically from tubercle bacilli by a competent technician. Care in sterilization of utensils and the use of sterile distilled water during the lavage will prevent contamination by other acid-fast organisms. Stadnichenko, Cohen and Sweany (2) have stated emphatically that "acid-fast bacilli in the stomach content are virulent and not indifferent saprophytes." Furthermore, in 176 of their patients who had no evidence of tuberculosis, no acid-fast bacilli were found by gastric lavage. Floyd, Novack and Page (3) also failed to find any acid-fast organisms in the stomach contents of 219 normal persons. Robinson and Dunn (4), in compiling the gross results in the literature up to 1943, found only one positive result in 903 nontuberculous persons. The possibility of accidental tubercle bacilli occurring in normal individuals is also eliminated by the same set of data.

Immunity of guinea pigs to the tubercle bacillus has been suggested recently by Franco and Gurevitch (5) as an explanation of negative results in guinea pigs inoculated with supposedly virulent tubercle bacilli. This factor, however, can be controlled adequately by the inoculation of a large amount of sediment from the centrifuged specimen, by the injection of several animals with the same

material, and by allowing a two-month period of observation before autopsy. Moreover, the culture plate will aid in identification of the bacilli in these cases.

Naturally avirulent or hypovirulent tubercle bacilli which fail to infect guinea pigs after employment of the precautions noted above are occasionally encountered, but are not a serious problem in diagnosis. Stadnichenko, Cohen and Sweany (2) found only one case in 211 in which the bacilli were of such low virulence that they failed to cause typical lesions when a heavy inoculum was used and the guinea pigs were observed for two months.

The most logical explanation of our anomalous findings is that the tubercle bacilli are acted upon by some agent in such a way as to destroy their pathogenicity for guinea pigs without rendering them unrecognizable microscopically. (In addition to the disparity between microscopic diagnosis and guinea pig diagnosis, it has been noted that many lavage specimens are reported to contain "numerous typical and atypical acid-fast bacilli." Although the morphology of the tubercle bacillus is known to be varied, the organisms recoverable in sputum examinations are rarely "atypical." This aspect of the problem is at present under investigation and will be reported at a later date.) Since guinea pigs usually develop tuberculosis when injected with sputum specimens which yield a positive smear, the agent responsible is probably in the gastric juice.

The effects of various agents have been studied without any satisfactory agreement among investigators. Roper and Ordway (6) showed that the presence or absence of bile in the gastric specimens had no influence on the results of animal inoculation. They also demonstrated that N/10 free hydrochloric acid (stronger than is ever found in the normal stomach) did not affect the viability of human tubercle bacilli after an exposure of forty hours. Inkster and Gloyne (7) incubated tuberculous sputum for one and a half hours in gastric juice with as much as 62 degrees acidity without destroying the virulence of the tubercle bacilli. Falk (8) as early as 1882 found that gastric juice did not kill the organisms in tuberculous material taken from human lungs at autopsy, but failed to state in his paper the time allowed for action of the gastric juice. Cadeac and Bourney (9) administered to dogs tuberculous material mixed with feed and were able to recover stainable and pathogenic organisms from the stomach and gastrointestinal tract twelve hours after feeding. The reviews of their paper do not state the findings of experiments lasting more than twelve hours, and the original paper is not available.

On the other hand, Bartle and Harkins (10) compared the pathogenicity of tubercle bacilli when introduced by mouth and when introduced intraperitoneally in guinea pigs. They found that the latter route resulted in more destructive tuberculous lesions and present this as an evidence of the bactericidal activity of the stomach. The strict validity of this conclusion may well be questioned. However, it is a well known clinical observation that tuberculosis of the stomach caused by ingesting or swallowing tubercle bacilli is extremely rare. Hence, it must be suspected that the bactericidal effect of gastric juice may have an influence on the pathogenicity of tubercle bacilli for experimental animals. Because of the confusion indicated by the reports in the literature and the indirect but

fairly substantial evidence suggesting gastric juice as the agent affecting the bacilli, investigation of this relationship seemed to be not only of scientific interest but of some practical importance.

EXPERIMENTAL PROCEDURE

It is unnecessary to discuss here the development of the gastric lavage and guinea pigs inoculation techniques for the diagnosis of pulmonary tuberculosis in adults. Poulsen and Anderson (11) have given a complete review of these techniques. Investigators in many foreign countries as well as in the United States have amply demonstrated the efficiency of these methods. Recent improvements in culturing the tubercle bacillus have given results as good as, but no better than, guinea pig inoculation (4). Since the number of positive results in culture and by inoculation has run almost exactly parallel in our series, it was felt that studies on guinea pigs alone would give results comparable to culture methods and at the same time conserve complex media. The frequency of culture contamination by rapidly growing organisms present in normal gastric juice and the possibility of the early use of the skin tuberculin reaction in the guinea pig method would seem to make the latter technique the more desirable.

The sputa of 3 patients with advanced pulmonary tuberculosis were collected and pooled. Microscopic examination of the sputa using the Ziehl-Neelsen stain showed the sputa to be loaded with many typical, thin, nodular, acid-fast bacilli. In order to limit the number of factors influencing the results, no concentration or liquefaction methods using acids or alkalis were used. (The routine use of these agents probably does not influence the pathogenicity of the organisms (1).) Injection of this specimen subcutaneously into the inguinal region of 2 guinea pigs produced typical visceral caseous lesions from which the organisms could readily be recovered at autopsy. A similar result was obtained with the control when the untreated sputum was incubated at 37°C. for sixty-five hours.

Gastric lavages were done before breakfast on 2 patients with no evidence of tuberculosis and no gastrointestinal lesions, and the specimens were pooled. The juice contained 22 degrees of free hydrochloric acid (calculated in terms of cc. of N/10 sodium hydroxide required for neutralization of 100 cc. of gastric contents). Injection of an untreated portion failed to produce any lesions suggestive of tuberculosis in 2 guinea pigs, and no organisms could be found after a careful search at autopsy.

Forty cc. of this normal gastric juice (about the average amount of residuum found during the interdigestive state) was mixed thoroughly with 5 cc. of tuberculous sputum and the mixture incubated at 37°C. At intervals throughout the incubation period, the mixture was shaken to simulate the motility of the stomach. From time to time 2 cc. of the mixture was withdrawn and injected subcutaneously into the left inguinal region of a guinea pig. Three animals were used for each time interval. Each group of 3 was isolated from the other groups. At the end of four weeks 0.2 cc. of a 1:1000 solution of Old Tuberculin was injected intracutaneously on the abdomen; the results were read in forty-eight hours. Two and a half months after inoculation the animals were autopsied

and smears made of both inguinal nodes, spleen, liver and, when suspicious, lungs. Gross demonstration of caseous tubercles and microscopic identification of the organisms with Ziehl-Neelsen stain were reported as positive (+). Absence of any organisms, lymphadenopathy or caseous tubercles was reported as negative (–). Slight lymph node enlargement or atypical organisms were reported as "plus-minus" (±). All utensils were carefully sterilized and sterile distilled water was used for washing. The techniques employed in the experiment, as well as the methods used in our hospital, are similar to those suggested by the American Trudeau Society Committee of Standard Procedure (1) and a 1941 symposium on the demonstration of tubercle bacilli giving the views of prominent investigators. The results are shown in table 1.

TABLE 1

Results of guinea pig inoculation

	INTRACUTANEOUS REACTION			GROSS ANATOMICAL FINDINGS			MICROSCOPIC FINDINGS		
	*1	2	3	1	2	3	1	2	3
CONTROLS:									
Untreated normal gastric juice	–	–		–	–		–	–	
Untreated tuberculous sputum	4+	4+		+	+		+	+	
Incubated tuberculous sputum	4+	4+		+	+		+	+	
MIXTURE: (Juice and sputum)									
Incubated:									
0 hours	4+	2+	4+	+	+	+	+	+	±
1 hour	4+	3+	1+	no autopsy	+	+	no autopsy	+	+
4 hours	3+	4+	4+	+	+	+	+	+	+
10 hours	1+	1+	±	+	+	±	+	+	–
21 hours	–	±	±	–	–	–	–	–	–
45 hours	–	–	–	–	–	–	–	–	–
68 hours	–	–	died	–	–	died	–	–	died

* 1, 2, 3 = Number of the animal in each group.

RESULTS

It may be seen from table 1 that tuberculous sputum exposed to normal gastric juice at body temperature for about ten hours began to lose its pathogenicity for

guinea pigs. After twenty-one hours the sputum was rendered completely innocuous. A more exact determination of this period of time could have been made, but was considered unnecessary and impractical, since the time needed for destruction of the bacilli will vary somewhat with the virulence of the organisms, the number present, the strength of the agent in the gastric secretions, the natural resistance of the guinea pigs used, and the temperature of incubation.

It is interesting to note that the findings confirm the work of Sayago (13) in that the intracutaneous tuberculin reaction, the gross findings at autopsy and the microscopic examination of suspicious lesions agree closely and serve as checks on each other.

The variability of the guinea pig response is demonstrated and emphasizes the necessity of using 2 or more animals for each specimen.

The tuberculin reactions varied quantitatively in each group and could not be used as evidence of the degree of infection present.

CONCLUSIONS

Under the conditions of the experiment, virulent tubercle bacilli in human sputum after incubation in normal human gastric juice for ten to twenty-one hours at 37°C. were rendered nonpathogenic for guinea pigs and could not be recovered from their organs at autopsy. The exact limit of retained pathogenicity will vary with each specimen. The clinical significance of these findings may be summarized as follows:

1. Since all of the patients considered had either early minimal infections or were merely suspected of having active tuberculosis, the number of bacilli reaching the stomach would be relatively small. Thus the action of the gastric juice would be more effective in preventing infection of guinea pigs by the bacilli. The incidence of "false negative" results would necessarily be higher, therefore, in cases of this type.

2. A few tubercle bacilli may remain in the stomach overnight (twelve or more hours) and give "false negative" guinea pig tests after being acted upon by the gastric secretions. This is especially likely in early cases in which only occasional showers of organisms appear in the stomach. Because of the comparatively rapid emptying time of the stomach, and the statistical infrequency of these results in the literature, this factor is probably an infrequent one.

3. Viable, virulent organisms recently swallowed and not yet removed as the result of gastric motility may lose their pathogenicity if not injected into guinea pigs within a few hours after aspiration. In our hospital, as in many hospitals at the present time, the technicians are overburdened with a multiplicity of wartime duties. Guinea pigs are often not inoculated until the following day, and some specimens may stand in the icebox or at room temperature over the weekend. The bacilli may be destroyed by the gastric juice, thus producing a "false negative" guinea pig test. This is not a problem in special institutions handling only tuberculous patients. In such institutions, rapid and efficient methods have been developed for the handling of a large number of specimens.

4. Since free hydrochloric acid of the concentration found in the human stomach is apparently ineffective in destroying the tubercle bacillus, either gastric

lipase acting in an acid medium or pepsin in the presence of hydrochloric acid are suggested as possible agents capable of destroying the pathogenicity of the organism. Further studies of this relationship will be reported in a later paper.

CONCLUSIONES

En las condiciones de este experimento, los bacilos tuberculosos virulentos que contenía el esputo humano mostráronse anapatógenos para los cobayos tras la incubación en jugo gástrico humano normal durante 10 a 21 horas a 37° C, y no pudieron aislarse de los órganos de éstos en la autopsia. Las cifras exactas de la patogenicidad retenida variaron en cada ejemplar. El significado clínico de estos hallazgos puede sumarizarse en esta forma:

1. Como todos los enfermos estudiados bien tenían, infecciones mínimas tempranas o eran meramente sospechosos de tuberculosis, el número de bacilos que llegaban al estómago debió ser relativamente pequeno, de modo que la acción del jugo gástrico sería más eficaz para impedir la infección bacilar del cobayo. En casos de este género la incidencia de "seudonegativos" sería por lo tanto forzosamente mayor.

2. Algunos bacilos tuberculosos pueden permanecer en el estómago durante la noche (12 hs. o más) y producir reacciones "seudonegativas" en el cobayo después de ser atacados por las secreciones gástricas. Esto es sobre todo, probable en los casos tempranos, en que sólo llegan al estómago lloviznas ocasionales de microbios. Debido al tiempo de vaciamiento comparativamente rápido del estómago y la rareza estadística de este fenómeno en la literatura, este factor también es probablemento raro.

3. Los microbios virulentos viables recién ingeridos y no retirados todavía por efecto de la motilidad gástrica, pueden perder su patogenicidad si no se les inyecta en el cobayo a las pocas horas de la aspiración. En el hospital donde se lleva a cabo este estudio, así como en muchos otros, los médicos se hallan actualmente sobrecargados con una multitud de tareas relacionadas con la guerra, de modo que los cobayos a menudo no son inoculados sino hasta el día siguiente y algunos ejemplares pueden permanecer en la nevera o a la temperatura ambiente todo el fin de semana. Los bacilos también pueden ser destruídos por el jugo gástrico dando así una reacción "seudonegativa" en el cobayo. Esto no constituye un problema en las instituciones especializadas que sólo atienden tuberculosos, pues en ellas se han elaborado técnicas rápidas y eficaces para el manejo de una gran cantidad de ejemplares.

4. Como el ácido clorhídrico libre a la concentración encontrada en el estómago humano es aparentemente ineficaz contra el bacilo tuberculoso, se han mencionado, como posibles agentes capaces de destruir la patogenicidad del microbio, la lipasa gástrica actuando en un medio ácido o la pepsina en presencia de ácido clorhídrico. En un trabajo subsecuente se describirán nuevos estudios de esta relación.

REFERENCES

(1) Committee on Standard Laboratory Procedure: Minimum laboratory standards in the diagnosis of tuberculosis, Am. Rev. Tuberc., 1942, *45*, 103.

(2) Stadnichenko, A., Cohen, S. J., and Sweany, H. C.: Stomach lavage in the diagnosis and control of treatment of tuberculosis, J. A. M. A., February 24, 1940, *114*, 634.
(3) Floyd, C., Novack, H. A., and Page, C. G.: Gastric lavage in healthy adolescents: Study of fasting contents for tubercle bacilli, Am. Rev. Tuberc., 1942, *46*, 622.
(4) Robinson, J. L., and Dunn, W. T.: Gastric lavage and sputum cultures, Am. Rev. Tuberc., 1943, *47*, 413.
(5) Franco, S. E., and Gurevitch, J.: Atypical findings on animal inoculation, Am. Rev. Tuberc., 1942, *46*, 625.
(6) Roper, W. H., and Ordway, W. H.: Gastric lavage in adults with pulmonary tuberculosis, Am. Rev. Tuberc., 1941, *43*, 543.
(7) Inkster, J., and Gloyne, S. R.: The bactericidal action of gastric juice on B. tuberculosis, Brit. M. J., December 17, 1921, *2*, 1024.
(8) Falk: Über das Verhalten von Infectionsstoffen im Verdauungkanal, Arch. f. path. Anat. Phys., 1882, *93*, 177.
(9) Cadeac and Bourney: Role microbicide des sucs digestifs et contagion par les matières fécales. La Province Méd., 1893, Vol. VIII, No. 28, p. 304. Quoted by Baumgarten's Jahresbericht, 1894, p. 574, and by Scheer in Arch. f. Hyg., 1919 88, 130.
(10) Bartle, H. J., and Harkins, M. J.: The gastric secretion: Its bactericidal value to man, Am. J. M. Sc., 1925, *169*, 373.
(11) Poulsen, V., and Anderson, A. D.: Four years' experience with examination of material obtained by gastric lavage, Am. J. Dis. Child., 1934, *47*, 307.
(12) Demonstration of Tubercule Bacilli, (Panel Discussion), Am. Rev. Tuberc., 1941, *44*, 487.
(13) Sayago: Value of examining gastric contents for tubercle bacilli, Rev. paulista de tisiol., 1940, *8*, 281.

ANATOMICAL STUDIES ON HUMAN TUBERCULOSIS[1]

XXII. Primary Foci without Lymph Node Changes

Additional Observations

KORNEL TERPLAN

In two previous papers (1) it was shown that primary tuberculous infection can restrict itself to one or more parenchymatous foci in the lung tissue without leading to further spread to any lymph node draining the area of the primary foci. The bronchomediastinal lymph nodes and intrapulmonary lymph nodules were free of tuberculous changes including active granulation tissue and fibrous-chalky or stony scars. The lymph nodes regional to the primary focus or foci were examined in complete serial sections in several cases of our previous series, which included in all 5 children and 21 adults. This represented 8.8 per cent of all (57) cases of children examined postmortem in which various tuberculous lesions were found (2), and between 8 and 9 per cent of 245 adult cases with tuberculous findings. It was stated in the concluding paragraph to one of our papers (XII) that this type of primary infection, restricted to a small parenchymatous lesion, should not be considered as exceptional or even as infrequent.

In the present paper additional observations will be reported to call attention once more to these primary foci without any trace of regional lymph node changes. The material used for this study is from the past five years. As there is hardly any other information available in the literature than our figures quoted above, it seemed of interest to learn how far our new observations might confirm or modify our previous impression as to the incidence of these small primary foci without any spread to lymph nodules, which presented such a striking exception to the law of Parrot. It was felt, also, that this type of tuberculous infection deserves the attention of all those pathologists who are interested in the exact incidence of tuberculous lesions found postmortem. The small and frequently minute size of these primary tubercles makes a most careful anatomical search imperative. Without postmortem X-ray photographs and without complete histological study of all the calcified structures seen radiographically and identified by dissection, obviously most, if not all, of these small primary foci would be missed. Any statistical study of the incidence of tuberculous lesions, not based on roentgenological and complete histological study, but merely on the usual routine macroscopic examination of the lungs, does not yield reliable figures. Apart from these small foci without lymph node changes, healed primary complexes with small parenchymal and lymph node components might also be overlooked. If the morphological analysis of our postmortem material of our present series has shown that, among nearly 100 cases between four and forty years of age, more than one-fourth represent this type of infection,

[1] From the Department of Pathology, Medical School, University of Buffalo, and the Pathology Laboratories of the General Hospital and Children's Hospital, Buffalo, New York.

it is clear that any future anatomical statistical study cannot ignore these primary foci without lymph node changes. Their incidence, as found in the postmortem material of general hospitals for adults and children, is far greater than might have been expected from the scarce notes in the literature which we quoted in our previous papers. Our findings are also of interest, as we have stressed repeatedly in the past, in regard to the tuberculin reaction of persons harboring small scars of first infection, entirely restricted to the lung tissue. It is probable that in most cases of our present series the tuberculin reaction would have been negative. The charts did not give any information on these data. A negative tuberculin reaction—in healthy persons of these younger age groups—indicates either the absence of any previous tuberculous infection or the presence of a practically inert, obsolete tuberculous scar of the primary focus or foci, or of entirely healed primary complexes. While these latter might be recognized on the chest film, the small foci restricted to the pulmonary parenchyma are apt to escape roentgenological recognition during life.

The material used for this study was taken only from children and adults of the second, third and fourth decade. We shall present our findings only in relation to the total incidence of tuberculous lesions in these age groups. All cases in which careful gross dissection of the respiratory and intestinal tract did not reveal any tuberculous lesions, either in the parenchyma or in the lymph nodules, in which, however, postmortem X-ray examination was not carried out, were excluded from our material. Whether these were actually negative or whether some might have harbored small primary foci without lymph node changes has to remain uncertain. It is possible that the incidence of these small parenchymatous primary lesions was actually higher in the entire postmortem material than it would appear from the selected material, including only those cases which were sufficiently studied by postmortem X-ray films. These alone will be used for our present discussion.

The findings in 5 children and 22 young adults are given on table 1. Plate 1 shows a low power field of the primary foci in 5 instances; the magnification is about 30×.

Only in 2 cases of the present series were the intrapulmonary and bronchomediastinal lymph nodes regional to the area of the parenchymatous focus examined in complete histological serial sections. Selected sections through various levels of the regional lymph nodes were made in 9 instances of the present series, including one child and 8 adults. In the remaining cases (3 children and 13 adults) there was no histological study of the intrapulmonary and bronchomediastinal lymph nodules. In all these latter cases, however, the lymph nodules were carefully examined and sliced. They were, in every single case, of normal size, soft and free of fibrous nodules or scars.

As to the structural state of these primary parenchymatous foci, they were caseous-chalky within a thin mesenchymal or already hyalinized capsule in 3 children, and firmly calcified in the 2 remaining cases of this group. In the adult group they were chalky-calcified in 4, in more pronounced state of calcification also in 4, and in firm stony-ossified state with a more or less typical bony ring in 14 instances.

TABLE 1

Primary focus or foci without lymph node changes

CHILDREN

CASE NUMBER	AGE, RACE, SEX	PRIMARY FOCUS OR FOCI			SPECIAL REMARKS
		Number	Size and location	Structural state	
C. H. 1132	4, White M	1	2 x 1 mm.; upper third, left upper	Caseous-chalky; hyaline capsule	
C. H. 666	9, White M	2	1 mm., each; upper third, right upper	Firmly calcified	Perifocal fibrosis
C. H. 1182	10, White F	1	1 mm.; lower third, right lower	Chalky-calcified; thin mesenchymal capsule (figure 1)	Calcified pulmonary duct
B. G. H. 2999	11 White F	1	2 mm.; lower third, left lower	Early calcification	Serial sections through lymph nodes
C. H. 1161	11½, White M	1	1–2 mm.; subapical portion, right upper	Calcified; fibrous capsule (figure 2)	
ADULTS					
5454	21, White F	1	1–1.5 mm.; right lower	Chalky-calcified	
5122	21, White M	1	2 mm.; right middle	Stony (figure 3)	
2941	23, Colored F	2	1 mm.; each; hilar area, right upper, left lower	Chalky-calcified	
2650	23, White F	1	1 mm.; subapical left upper	Stony-ossified, marrow	
5045	25, White F	3	0.8–1.5 mm.; right lower and right middle	1 firmly ossified 2 fibrocalcified	
4763	25, White F	2	2 mm., 3 mm.; middle third left upper, right middle	Stony-ossified (figures 4 and 5)	Serial sections through lymph nodes

TABLE 1—*Continued*

CASE NUMBER	AGE, RACE, SEX	PRIMARY FOCUS OR FOCI			SPECIAL REMARKS
		Number	Size and location	Structural state	
ADULTS					
5777	25, White M	1	2 mm.; middle third, right lower	Calcified	
5404	26, White M	2	2 mm., each; right upper	Stony-ossified	
5257	26, White F	1	1–1.5 mm.; left lower	Stony, thin bony ring	3 osteomatas i' right lower
5239	26, White F	1	1 mm.; right lower	Calcified	Phlebolith; 2 osteomata
5114	26, White F	1	0.8–1 mm.; upper third, left lower	Chalky-calcified	Calcified pulmonary duct
5214	27, White F	1	1–1.5 mm.; right upper	Calcified, bony shell	
5736	27, White M	5	1–1.5 mm., each; 4 in right middle and lower third right upper; 1 in upper third left upper	Calcified-ossified	
5742	27, White F	2	0.5, 0.9 mm., each; subapical area (symmetrical)	Stony-ossified	1 osteoma, 2 mm.
5213	28, White F	1	2 mm.; upper third left lower	Stony, bony ring (figure 6)	
5657	30, White M	8	1–2 mm., each; 4 in left lung; 4 in hilus level, right lung	Firmly stony, one with some bone	
4665	31, White F	4	1 mm., each right upper, right lower, left lower	Stony-ossified	

TABLE 1—*Continued*

CASE NUMBER	AGE, RACE, SEX	PRIMARY FOCUS OR FOCI			SPECIAL REMARKS
		Number	Size and location	Structural state	
ADULTS					
5774	31, White M	1	1 mm.; middle third, left upper	Calcified. Langhans' giant cells in periphery	
2373	35, White F	1	2 mm.; lower third, left lower	Fibrous scar-chalky	
4864	37, White F	1	2 mm.; lower half, left lower	Stony-ossified	
5660	37, White M	2	Slightly less than 1 mm.; right middle and upper third left lower	Calcified-ossified, hyaline wall	
4933	38, White M	1	0.5–1 mm.; apex, right upper	Calcified, fibrous wall	

We add to this table 2 cases which, from the gross anatomical appearance, were thought to belong to the same group. Histological study of all calcified tubercles found in the parenchyma proved that in both there were calcified tubercles in intrapulmonary lymph nodules regional to the parenchymatous foci. One was seen in a child 9½ years old, the other in a colored female 46 years of age (these 2 cases are not included in our discussion):

C. H. 1123	9½, White M	5	1 mm.; 2 in right lung, 3 in left lung	Calcified, thin fibrous capsule	2 calcified lymph nodules, right lung; 1 calcified lymph nodule, left lung—1 and 2 mm. A few osteomata
B. G. H. 2114	46, Colored F	2	2 mm.; upper third left upper; bases right lower	Stony-ossified; stony-chalky	1 subpleural fibrous conglomerate tubercle, right middle (lymph nodule)

As to the number of these primary foci, they were single in 17 cases (including 4 children); there were 2 in 6 cases (including one child); and 3, 4, 5 and 8,

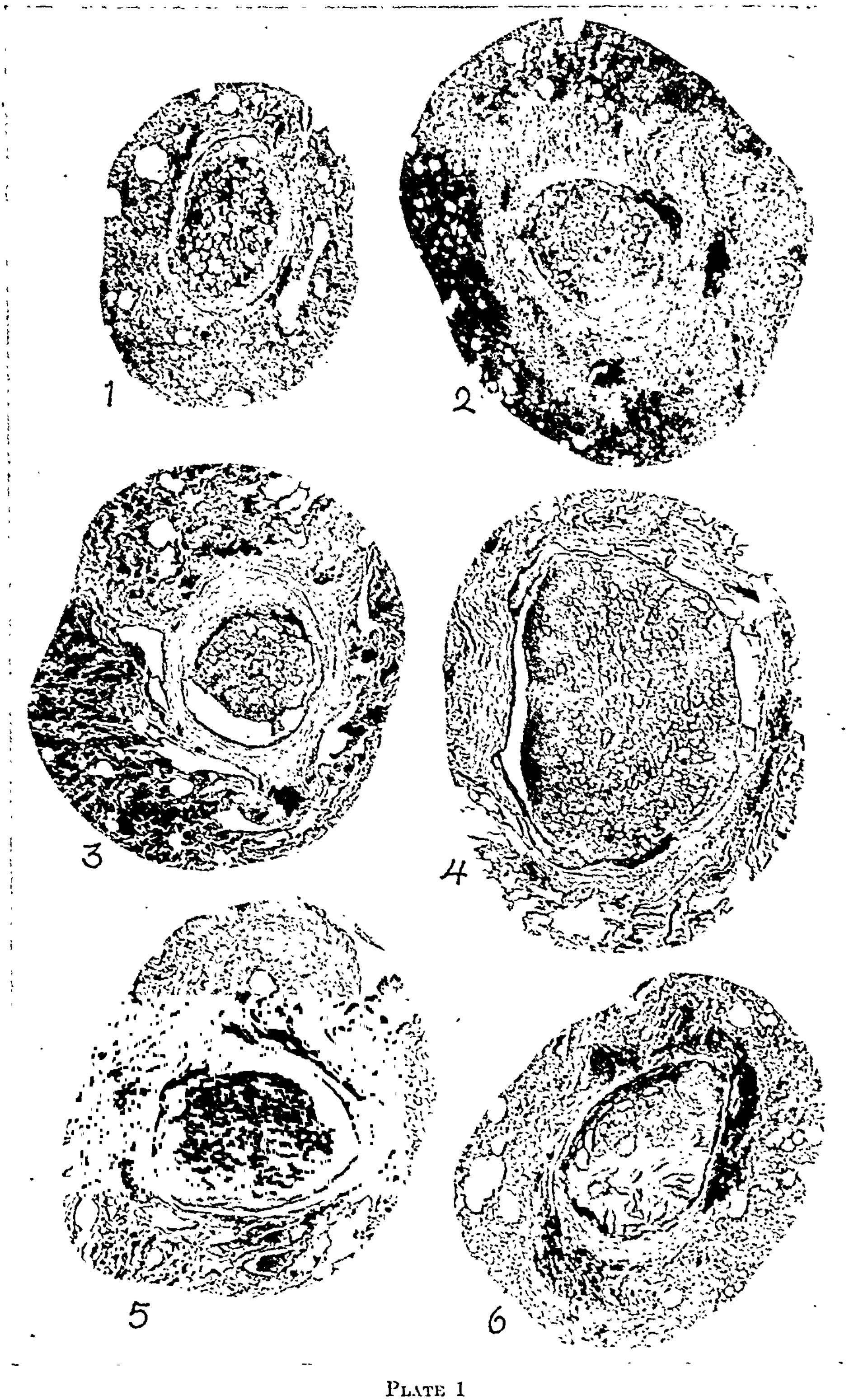


PLATE 1

respectively, in the remaining cases—all in the adult group. The location of these parenchymatous lesions is in no way different from that observed in typical primary infections. The middle field appears as the preferred site. The figures are as follows: *upper field:* left 3, right 5; *middle field:* left 9, right 14; *lower field:* left 7, right 4. Only in one instance was the primary focus in the apex (the actual summit) of one upper lobe. It was a minute calcified stone within a firm fibrous wall.

In the cases with two primary foci the lesions were in the same lobe in 2, at fairly symmetrical levels in both lungs in 3, and at distinctly different levels of both lungs in one case. In the 4 cases with more than two foci the location included various areas of both lungs. The sizes of these small lesions, given in column 5 of the table, indicate the diameters of the tubercles in the stained sections. Only one focus had a diameter of 3 mm.; the majority were between 1 and 2 mm., while in one lesion (No. 5742) the diameter was slightly below 1 mm. It is in this case that an "osteoma" was also revealed by the X-ray photograph.

TABLE 2

VARIOUS TUBERCULOUS CHANGES—EXCLUDING PRIMARY FOCI WITHOUT LYMPH NODE CHANGES		PRIMARY FOCI WITHOUT LYMPH NODE CHANGES	
Age groups	Number of cases	Age groups	Number of cases
5–10 years	7	5–10 years	3
11–20 years	12	11–20 years	2
21–30 years	15	21–30 years	16
31–40 years	35	31–40 years	6
	69		27

It was of smaller size (2 mm.) than the two symmetrical primary foci in each subapical field. Other calcified lesions of nontuberculous nature included two "osteomata" and one phlebolith in one case, three "osteomata" in another, and a calcified thrombus in the pulmonary duct in 2 cases. The minute size of all these calcified structures, especially if found in the same case (combining a true primary focus, a phlebolith and two "osteomata," all between 1 and 2 mm. in size), makes histological study indispensable. It is frequently impossible to differentiate these lesions with the unaided eye, especially if they are only 1 or 2 mm. in thickness. Although the size of these primary tubercles is obviously small, a comparison with the figures of the healed primary foci in all those cases in which a reinfection complex had occurred (3) reveals that the majority of these old foci of first infection did not exceed 2 mm. in diameter, 22 were between 1 and 2 mm., and 12 between 2 and 4 mm.

Among 19 cases with various tuberculous lesions in children below four years of age, there was no instance with a single focus without tuberculous lymph node changes.

The relation of our cases with these single foci without spread to lymph nodes to the other more usual anatomical types of tuberculous lesions in our selected material, including all positive cases found in these age groups, is seen in table 2.

The 69 positive cases listed in column 2 included 22 with progressive fatal tuberculosis, 45 with a closed chalky or calcified primary complex and 2 with two complexes of different age.

If only the 5 cases of the children's group (table 1) are related to our entire material of 37 cases (from nine months to sixteen years) with various types in children alone—which will be discussed in one of the forthcoming papers—of tuberculous lesions the percentage of foci without lymph node changes is 13.5—somewhat in excess of the figure in our previous series in children, which was 8.8 per cent.

It is obvious that the incidence of primary foci without lymph node changes in these selected younger age groups is distinctly higher than in the material presented in the previous paper in which all adult groups were included, with 6 instances from cases above forty years of age. Our present figures, therefore, are hardly comparable with the former series. As the time of infection cannot be accurately estimated from the histological structure alone, especially in the obsolete state in which most of these primary tubercles in our adult group were found, no comment seems advisable on the surprisingly high incidence of foci without lymph node changes in the third decade. These cases exceeded those with various other tuberculous findings, including 4 instances with fatal progressive primary, or reinfection tuberculosis, 2 with a reinfection complex and 9 with a closed primary complex. There was a relatively large death rate of young adults, previously in the best of health, in the second and third decade, who had succumbed to the poliomyelitis epidemic in the summer and fall of 1944. Most of them were either entirely free of any tuberculous lesion or harbored these single foci without lymph node changes.

In the course of our systematic morphological studies of tuberculous lesions in adults, it was learned that anatomical effects of the first tuberculous infection might be incidentally encountered in an increasing number of young adults, and that frequently the structural state of the primary tubercles and the changes in the regional lymph nodes suggested strongly that they were acquired well beyond the age of puberty. It is in part for this reason that in the last five years our search for the incidence and type of tuberculous lesions has centred more about the younger age groups. In these it is unlikely that a calcified primary tubercle, once established in the pulmonary parenchyma, should be completely resorbed. That occasionally a primary caseated tubercle might be entirely organized by fibrous tissue is certain, but even these fibrous scars seem to persist in a more or less calcified state. This fibrous organization, however, is, on the basis of our experience in many hundreds of cases, the exception rather than the rule.

The morphological analysis of the 27 cases in this series, with one or more primary foci without lymph node changes, represents a percentage of 28.1 out of a total of 96 cases with anatomical findings of tuberculosis. From this it can be concluded that such minimal primary tuberculous infections of the lung tissue are not uncommon at all. They prove that primary infections can heal *in situ* without involving regional lymph nodules and lymph nodes. That such a successful healing at the site of the primary lesion by complete encapsulation

and scar formation is not necessarily a protection against a reinfection was shown in a few instances published in previous papers on the reinfection complex. In some of these the size of the primary focus was just as small as in the cases of this series, and there was no spread from this focus to the regional lymph nodes. Yet, a rather typical complex of reinfection had formed which was found in a comparatively recent state, with massive involvement of the lymph nodes. Whether or not one is justified to postulate slight (abortive) infections caused by a relatively small number of bacilli as the main causative factor for these restricted tissue reactions and the small size of these primary tubercles cannot be stated with any degree of certainty on the basis of our findings. The factor of successful resistance of the host tissue appears of no less importance.

It is possible that this apparent increase of such small primary tubercles restricted to the lung tissue reflects the declining trend in the incidence of tuberculous infections in general and of those leading to progressive disease in particular.

There were hardly any studies carried out in the past, especially in nonmetropolitan cities, which could serve as comparable material for the figures reported in this paper. Detailed systematic anatomical and histological observations, including particularly postmortem X-ray photographs, are not available in any comparable manner in the tuberculosis literature. It is possible that these small primary foci without lymph node changes might have been present but not recognized—because not anticipated—by the pathologist whenever no tuberculous lesions were found in any lymph node group.

SUMMARY

Additional observations of primary foci without lymph node changes, incidentally found in 5 children and 22 young adults, are reported. These figures represent about 28 per cent of a total of 96 cases with various findings of tuberculosis in children between four and sixteen years of age, and in adults from twenty to forty years. Number, size, location and structural state of the primary foci are listed in table 1; their numerical relation to the cases with a variety of tuberculous lesions, including progressive fatal tuberculosis and the usual picture of the closed primary complet, is presented—in corresponding age groups—in table 2.

Anatomical statistics as to the exact incidence of tuberculous lesions as found postmortem in general and children's hospitals will prove more reliable if such cases with a small primary focus or foci without a lymph node complex are not overlooked. They are by no means uncommon.

SUMARIO

Preséntanse nuevas observaciones de focos primarios sin alteraciones ganglionares, descubiertos fortuitamente en 5 niños y 22 jóvenes. Estas cifras representan aproximadamente el 28% de un total de 96 casos con varios hallazgos de tuberculosis en niños de 4 a 16 años de edad y adultos de 20 a 40 años. Por grupos de edades correspondientes, enuméranse en la tabla 1: el número, tamaño, localización y estado histológico de los focos primarios; y en la tabla 2 su relación

numérica con los casos en que existen varias lesiones tuberculosas, incluso tuberculosis letal evolutiva y el cuadro habitual del complejo primario cerrado.

Las estadísticas anatómicas en cuanto a la incidencia exacta de las lesiones tuberculosas, tales como se encuentran en la autopsia en general y en los hospitales de niños, resultarán más fidelignas si no pasan por alto los casos, que no son muy raros, en que existen uno o más pequeños focos primarios sin complejo ganglionar.

REFERENCES

(1) Terplan, K.: Supplement to Am. Rev. Tuberc., vol. *42*, August, 1940; III. Primary tuberculous pulmonary foci without lymph node changes, p. 44. XII. Primary tuberculous focus without lymph node changes in adults, p. 168.

(2) Terplan, K.: Supplement to Am. Rev. Tuberc., vol. *42*, August, 1940: II. Incidence and anatomical types of tuberculosis in children, p. 14.

(3) Terplan, K.: The reinfection complex: Additional observations, Am. Rev. Tuberc., 1946, *53*, 137.

PRELIMINARY PROGRAM

Joint Annual Meetings

National Tuberculosis Association—42nd Annual Meeting
American Trudeau Society—41st Annual Meeting
National Conference Tuberculosis Secretaries—24th Annual Meeting

BUFFALO, NEW YORK—JUNE 10–13, 1946

All meetings will be held at the Statler Hotel

Monday, June 10

9:30 a.m.

Registration
National Tuberculosis Association
  Committee on Qualifications
  Committee on Archives
National Conference of Tuberculosis Secretaries
  Meetings of Advisory Committees
  Personnel Practices Committee
American Trudeau Society
  Council Meeting

2:00 p.m.

National Tuberculosis Association
  Joint Committee on Seal Sale Percentages
  Advisory Committee on Motion Pictures
National Conference of Tuberculosis Secretaries
  Executive Committee
American Trudeau Society
  Council Meeting

3:00 p.m.

Conference on Heart Disease Programs by Tuberculosis Associations
  (Program to be announced)

Tuesday, June 11

9:30 a.m.

American Trudeau Society
  Ezra Bridge, M.D., Rochester, N. Y., *Chairman*
  Business Meeting, including reports of the following:
    Report of the President
    Report of the Secretary-Treasurer
    Committee Reports:
      Clinic Procedure
      Coexistent Syphilis and Tuberculosis

Coöperation with the American Board of Internal Medicine
Evaluation of Laboratory Procedures
Medical Advisory Committee on Health Education
Medical Information
Medical Program
Membership
Pan-American Relations
Policy
Postgraduate Medical Education
Rehabilitation
Revision of Diagnostic Standards
Sanatorium Planning and Construction
Therapy
Tuberculosis among Hospital Personnel
Tuberculosis in Industry
Tuberculosis in Mental Hospitals
Undergraduate Medical Education
X-ray Apparatus and Technique
Nominations
Election of Officers and Council Members

National Conference of Tuberculosis Secretaries

EDWARD K. FUNKHOUSER, Washington, D. C., *Chairman*
Business Meeting, including reports of the following:
Advisory Committees:
Administrative Practice
Health Education
Public Relations
Rehabilitation
Seal Sale
Bulletin Committee
Joint Committee on Programs of Tuberculosis Associations
Joint Committee on Seal Sale Percentages
Report of Secretary
Advisory Committee on Motion Pictures
Personnel Practices Committee
Purposes and Objectives of the Conference
Constitutional Amendment
Report of Treasurer
Nominations and election

2:00 p.m.

Medical Section

Advances in Roentgenologic Equipment
RUSSELL H. MORGAN, M.D., Tuberculosis Control Division, U. S. Public Health Service, Washington, D. C.

Treatment of Pleural Effusion by Frequent Aspiration
KIRBY S. HOWLETT, M.D., Laurel Heights Sanatorium, Shelton, Conn.

Factors Affecting the Growth of the Tubercle Bacillus
BERNARD D. DAVIS, S. A. Surgeon, U. S. Public Health Service, and RENE J. DUBOS, M.D., Rockefeller Institute, New York, N. Y.

Trends in Thoracic Surgery in the Treatment of Tuberculosis:
Review of Recent Trends—Summary of Meeting, American Association for Thoracic Surgery
RICHARD H. MEADE, JR., M.D., Chicago, Ill.
Experience in Thoracic Surgery in War Time
WM. M. TUTTLE, M.D., Detroit, Mich.
The Treatment of Pulmonary Tuberculosis by Resection
RICHARD H. OVERHOLT, M.D., N. J. WILSON, M. D. and J. T. SZYPULSKI, M.D., Boston, Mass.
Lobectomy and Pneumonectomy for Pulmonary Tuberculosis
RICHARD H. SWEET, M.D., Boston, Mass.
Discussion to be opened by HERBERT C. MAIER, M.D., New York, N. Y.

Public Health Section
ROBERT W. OSBORN, New York, N. Y., *Chairman*
What's New and News—Headline Interest in Bridging the Gap of Two Years Between Annual Meetings of the National Tuberculosis Association
In the Seal Sale.................GLENN V. ARMSTRONG
In Tuberculosis Statistics.................MARY DEMPSEY
In Local Organization.................PANSY NICHOLS
In Personnel.................GEORGE J. NELBACH
In Health Education
(a) *Adult*.................H. F. KILANDER, Ph.D.
(b) *School*.................VIVIAN V. DRENCKHAHN
In Group Chest X-raying.................WILLIAM A. DOPPLER, Ph.D.
In Public Health Nursing.................MARGARET S. TAYLOR, R.N.
In Rehabilitation.................HOLLAND HUDSON
In Social Developments in Behalf of Tuberculosis Patients.................BAILEY B. BURRITT
In Scientific Developments.................H. CORWIN HINSHAW, M.D.

4:30 p.m.

National Tuberculosis Association
Board of Directors Meeting

8:00 p.m.

General Meeting of the National Tuberculosis Association
Report of the Committee on Nominations
Award of the Trudeau Medal
Address of the President
Report of the Executive Office

Wednesday, June 12

9:30 a.m.

Medical Section
Evaluation of Cardiovascular Abnormalities Noted in Roentgenographic Surveys
HOWARD WEST, M.D., Los Angeles, Calif., and WM. PAUL THOMPSON, M.D., Los Angeles, Calif.
Antigenic Properties of the Carbohydrate Fraction of the Tubercle Bacillus
SIDNEY RAFFEL, M.D., Stanford University, Calif.

Vaccination of Nurses in Training in General Hospitals and of Sanatorium Employees
R. G. Ferguson, M.D., Fort San, Saskatchewan, Canada
Discussion to be opened by Joseph D. Aronson, M.D., U. S. Public Health Service, Washington, D. C.
Studies in Streptomycin:
Streptomycin in Experimental Tuberculosis
Wm. H. Feldman, D.V.M., M.S., and H. Corwin Hinshaw, M.D., Ph.D., Mayo Clinic, Rochester, Minn.
Streptomycin in Clinical Tuberculosis
H. Corwin Hinshaw, M.D., Ph.D., and Wm. H. Feldman, D.V.M., M.S., Mayo Clinic, Rochester, Minn.
Discussion to be opened by William Steenken, Jr., Trudeau Sanatorium, Trudeau, N. Y.

Public Health Section

Bruce H. Douglas, M.D., Department of Health, Detroit, Mich., *Chairman*
Making the Most of Group Chest X-ray Services:
Review of Relative Values of Tuberculosis Case-Finding Procedures
Robert E. Plunkett, M.D., State Department of Health, Albany, N. Y.
Group X-raying and Follow-up and Follow-through:
(a) *In a State*...................... C. W. Kammeier, Iowa
(b) *In a Large City*................. Charles Kurtzhalz, Philadelphia, Pa.
(c) *In a Local Area*................. speaker to be selected
(d) *Panel: Rochester—Monroe County, N. Y. Experience*
William A. Sawyer, M.D., *Chairman*
County Sanatorium Superintendent....... Ezra Bridge, M.D.
City Health Officer...................... Albert D. Kaiser, M.D.
Medical Society Representative........... Paul W. Beaven, M.D.
Tuberculosis and Health Association....... Marie Goulett
Community Groups..................... Mrs. Frank Gannett
Industry............................. to be selected

2:00 p.m.

Medical Section

Histoplasmin Sensitivity
Michael L. Furculow, M.D., Tuberculosis Control Division, U. S. Public Health Service, Washington, D. C.
Medical Mangement of the Recovery Phases of Tuberculosis:
Medical Prognostic Criteria
E. S. Mariette, M.D., Glen Lake Sanatorium, Oak Terrace, Minn.
Practical Experience with "In-Sanatorium" Rehabilitation Work
I. D. Bobrowitz, M.D., Municipal Sanatorium, Otisville, N. Y., and Arthur N. Aitken, M.D., Niagara Sanatorium, Lockport, N. Y.
Newer Knowledge in Air-Borne Infection:
Methods for the Control of Air-Borne Infection
O. H. Robertson, M.D., University of Chicago, Chicago, Ill.
Experimental Air-Borne Tuberculosis
Max B. Lurie, M.D., Henry Phipps Institute, Philadelphia, Pa.
Discussion

Public Health Section

Tuberculosis Associations: To-day and To-morrow
A group of delegates returning from the 1946 NTA Annual Meeting in Buffalo

are discovered in the parlor car of a streamliner. Their vigorous comment on what they have heard at Buffalo and their convictions as to what the Tuberculosis Association of "To-day and To-morrow" should be, and what it should do, are of interest to "fellow passengers."

Participants:
William P. Shepard, M.D., *Chairman*
Former president of the California Tuberculosis and Health Association, San Francisco, Calif. (Insurance Executive)
William Martin, president, Norfolk County Health Association, Quincy, Mass. (Banker)
Mrs. Elizabeth Semenoff, school health director, District of Columbia Tuberculosis Association, Washington, D. C.
Frank L. Jennings, M.D., Superintendent, Sunnyside Sanatorium, Indianapolis, Ind.
A. H. Aaron, M.D., representative of the Buffalo and Erie County Tuberculosis Association
(Other participants to be selected)

4:30 p.m.

National Tuberculosis Association
Board of Directors Meeting
National Conference of Tuberculosis Secretaries
Tea Dance

8:00 p.m.

Clinical Roentgenological Conference
Co-Chairmen, Chesley Bush, M.D., Arroyo Del Valle of Alemada County, Livermore, Calif., and M. C. Sosman, M.D., Professor of Roentgenology, Harvard University, Boston, Mass.
Panel: J. Burns Amberson, M.D., Bellevue Hospital, New York, N. Y.
John B. Barnwell, M.D., Veterans Administration, Washington, D. C.
Leo Rigler, M.D., University of Minnesota, Minneapolis, Minn.
John H. Skavlem, M.D., Cincinnati, Ohio

Thursday, June 13

9:30 a.m.

Medical and Public Health Sections, Joint Session
The Policies of the Veterans Administration with Regard to Medical Care
Major General Paul R. Hawley, Surgeon General, Veterans Administration, Washington, D. C.
Highlights in the Report of the Committee on Tuberculosis among Veterans
Herbert R. Edwards, M.D., Department of Health, New York, N. Y.
New Developments in the Tuberculosis Control Division, U. S. Public Health Service
Herman E. Hilleboe, M.D., Chief of Division, U. S. Public Health Service, Washington, D. C.
International Health Relations
James A. Doull, M.D., U. S. Public Health Service, Washington, D. C.

A Résumé of the Tuberculosis Experience of the U. S. Army—World War II
ESMOND R. LONG, Colonel, Medical Corps, Office of the Surgeon General, Army Service Forces, Washington, D. C.

12:30 p.m.

General Meeting of the National Tuberculosis Association
Brief talks by the incoming presidents of the National Tuberculosis Association, the American Trudeau Society and the National Conference of Tuberculosis Secretaries

1:00 p.m.

New York State Committee on Tuberculosis and Public Health of the State Charities Aid Association
Annual Meeting

2:00 p.m.

American Trudeau Society
Council Meeting
National Conference of Tuberculosis Secretaries
Executive Committee Meeting
Conference on Tuberculosis Nursing
JEAN SOUTH, R.N., *Chairman*
Supervisor, Community Service Organization, New York, N. Y.
(Program to be announced)
Adjournment

NOTICE

United States Public Health Service

February 11, 1946

Examinations for appointments of medical officers in the Regular Corps of the United States Public Health Service will begin on April 4 at various convenient localities throughout the country, Surgeon General Thomas Parran has announced. Examinations are for appointments to fill vacancies of Assistant Surgeon (First Lieutenant) and Senior Assistant Surgeon (Captain).

Regular Corps appointments are permanent. They provide qualified doctors with opportunities for a career in one or more of a number of fields including research, general hospitals, special hospitals, foreign duty, and public health programs. Assignments are made according to careful consideration of the officers' demonstrated abilities and experiences. It is expected that doctors now leaving the armed services will find the openings of particular interest.

Entrance pay for Assistant Surgeon with dependents is $3,411 a year, and for Senior Assistant Surgeon with dependents is $3,991 a year. Promotions are at regular intervals up to and including the grade of Medical Director which corresponds to full Colonel at $7,951 a year. Retirement pay at 64 is $4,500 a year. Full medical care including disability retirement at three-fourths pay is provided. All expenses of official travel are paid by the Government. Thirty days' annual leave with pay is provided.

Applicants for the grade of Assistant Surgeon must be citizens of the United States, must present diploma of graduation from recognized medical school, must have had or be in the process of completing the seventh year of college or professional training or experience since high school graduation (two years premedical, four years of medicine, one year internship), and must have a physical examination at the place of oral examination by medical officers of the Service. Applicants for the grade of Senior Assistant Surgeon must meet the above requirements and must have had four additional years of postgraduate training or experience.

Examinations will be oral and written. The written examination will be held on May 14, 15 and 16 at places convenient to the candidate and the Service. National Board grades may be used for the Assistant Surgeon examination. The oral examination will be held at 9 a.m. at the places and dates listed below:

Atlanta, Georgia—Malaria Control in War Areas, 605 Volunteer Bldg.	April 22
Baltimore, Maryland—Marine Hospital, Wyman Park Drive & 31st Street	May 9
Boston, Massachusetts—Marine Hospital, 77 Warren Street (Brighton)	May 6
Chicago, Illinois—Marine Hospital, 4141 Clarendon Avenue	April 30 May 1
Cleveland, Ohio—Marine Hospital, Fairhill Road & E. 124th Street	May 3
Denver, Colorado—617 Colorado Bldg.	April 8
Detroit, Michigan—Marine Hospital, Windmill Pointe	May 2

Fort Worth, Texas—U. S. Public Health Service Hospital................	April 25
Kirkwood, Missouri—near St. Louis—Marine Hospital, 525 Couch Ave....	April 26, 27
Los Angeles, California—USPHS Relief Station, 406 Federal Building.....	April 9
Minneapolis, Minn.—Office of Indian Affairs, 218 Federal Office Bldg......	April 29
New Orleans, Louisiana—Marine Hospital, 210 State Street..............	April 23, 24
New York, New York—Marine Hospital, Stapleton, Staten Island........	May 7, 8
Norfolk, Virginia—Marine Hospital, Hampton Blvd., Larchmont.........	May 10
San Francisco, California—Marine Hospital, 14th Ave. & Park Blvd.......	April 10, 11
Seattle, Washington—Marine Hospital, Judkins St. & 14th Ave. South....	April 12, 13
Washington, D. C.—USPHS Dispensary, Fourth and D Streets SW.......	April 4 May 13

Application forms may be obtained by writing to the Surgeon General, U. S. Public Health Service, Washington 25, D. C.

NOTICE

American Public Health Association

Institutions accredited by the American Public Health Association to give the Degree of Master of Public Health (Diploma of Public Health in Canada) for the academic year 1946–47

This list is released by the Executive Board of the American Public Health Association as of January 25, 1946, on recommendation of the Committee on Professional Education, and considers those institutions from which requests for accreditation had been received to that date. Additional applications will be acted upon in due course.

Columbia University School of Public Health
Harvard University School of Public Health
The Johns Hopkins School of Hygiene and Public Health
University of California School of Public Health
University of Michigan School of Public Health
University of Minnesota School of Public Health
University of North Carolina School of Public Health
University of Toronto School of Hygiene
Yale University School of Medicine, Department of Public Health

IMMUNIZATION WITH THE VOLE BACILLUS[1]

The Protective Value of the Vole Bacillus (Wells) as Compared with BCG against Tuberculous Infection

KONRAD BIRKHAUG

"Among the basic medical researches interrupted by the present European war," stated an editorial in the J. A. M. A. of February 8, 1941 (1), "none are of greater clinical interest than the Oxford University studies (2) of the vole acid-fast bacillus as a prophylactic vaccine against human or bovine tuberculosis. Although the experimental evidence thus far collected by Wells and Brooke is regarded by them as statistically inconclusive, their evidence is nevertheless sufficiently striking to warrant the hope that the vole vaccine may in time prove to be of clinical value."

In 1937 Wells (3) observed, at the Bureau of Animal Population in the University of Oxford, an epizootic disease among wild voles (*Microtus agrestis*) brought to the laboratory from seven different stations in the British Isles. The disease closely resembled tuberculosis. The caseous lesions in wild voles contained masses of acid-fast bacilli which on further study proved to represent a new type of tubercle bacillus.

The late A. Stanley Griffith (4) cultured the vole acid-fast bacillus and found that it grows dysgonically on the usual nonglycerinized egg media as pearly-white conical or granular colonies. These become visible to the naked eye after one month. The vole bacillus grows well on potato, but not at all on 5 per cent glycerine-agar or egg media. Slight filmy colonies appear on tryptinized broth, but not on the surface of plain broth. In the depth of broth a fine deposit forms. No growth occurs at 22°C. The vole bacillus stains positive with Gram and Ziehl-Neelsen methods. The bacilli are slender and much longer than ordinary human tubercle bacilli. The most striking forms resemble a shepherd's crook, a sickle, a spiral or the letter S. No branched forms are seen. Some bacilli show fine granulation and vacuolation along their entire length. Relatively large doses (1.0–0.1 mg.) of vole bacilli injected intravenously in rabbits cause death from acute miliary tuberculosis. Smaller intravenous or subcutaneous doses produce trivial lesions and the bacilli die out. The vole bacilli may live as long as eighty-four days in lung abscesses. Relatively large doses (1.0–0.1 mg.) of vole bacilli injected intraperitoneally in guinea pigs cause death from a generalized disease resembling acute or atypical chronic tuberculosis. Under the microscope the lesions have the pattern of tuberculosis. The lesions are retrogressive and those produced by small intraperitoneal or large subcutaneous (5 mg.) doses heal completely and yield no positive cultures. White rats injected intraperitoneally with 1.0 to 5.0 mg. vole bacilli may present lung lesions resembling those produced in the same species by mammalian tubercle bacilli. Vole bacilli may keep alive in the spleen of the rat as long as 493 days without

[1] From the Department of Medical Research, Chr. Michelsen Institute, Bergen, Norway.

killing the animal. The golden hamster (*Cricetus auratus*), injected subcutaneously with the vole bacillus, presented numerous noncaseous lesions in the liver, spleen and lymph nodes. These lesions have the histological pattern of tuberculosis. The fowl showed no ill effect from large doses of vole bacilli and live cultures of the bacillus could be obtained from the fowl spleen as late as 141 days after inoculation. It is quite apparent from Griffith's studies that the virulence of the vole bacillus is considerably higher than that of the BCG vaccine.

In their immunity experiments on calves injected with the vole bacillus, Griffith and Dalling (5) made preliminary inoculations into guinea pigs. Thus, 10 animals were injected subcutaneously with 10 mg. vole bacilli divided in nine doses (eight of 1 mg. and the last of 2 mg.). The intervals between consecutive doses were one week. Four weeks after the last dose, the immunized animals, together with 5 controls, were each injected subcutaneously with 0.001 mg. virulent bovine tubercle bacilli. The controls died of typical and severe generalized tuberculosis in from sixty-seven to 111 days, or an average of eighty-seven days. One of the vaccinated animals was killed after sixty-eight days to compare with the control animal which first died. This animal had severe local tuberculosis, but only slight generalized disease. The rest of the immunized animals died after 109 to 225 days, or an average of 152 days. The tuberculosis was severe in all these guinea pigs and was typical of infection with virulent bovine bacilli. The effect of vaccination was simply to delay the development of tuberculosis. This experiment was repeated with 8 guinea pigs which had received subcutaneously during eight weeks two doses each of 1 mg. and five doses each of 2 mg. vole bacilli or 12 mg. in all. One day after the last injection, the vaccinated and 4 control animals were each injected with 0.01 mg. bovine tubercle bacilli. Again, all the vaccinated animals were found to be more resistant to tuberculosis than the controls. Griffith and Dalling made the following significant statement based on these experiments: "They all, however, had living bovine tubercle bacilli in their tissues and there is little doubt that these bacilli would have caused progressive fatal disease when the immunizing effect of the vole bacilli had faded."

This led to similar vaccination of 9 calves injected intravenously or subcutaneously with smaller (0.1 mg.) or larger (85 mg.) doses of vole bacilli on two occasions and superinfected with 7.5 mg. bovine tubercle bacilli *per os*. Five calves presented trivial lesions in the lymph nodes of the alimentary tract. Four calves presented no macroscopic tuberculous lesions in any lymph nodes or organ. But living tubercle bacilli, pathogenic for guinea pigs, were nevertheless isolated from organs of these calves which presented no tuberculous lesions. Two control calves showed wide-spread glandular lesions, especially along the alimentary tract.

While this work was in progress, Wells and Brooke (2) made their preliminary tests of the immunizing power of caseous material taken from naturally infected wild voles. This they injected subcutaneously into 3 guinea pigs. Each animal developed a local caseous lesion. Nine months afterwards when the local lesion was completely healed, these animals were injected, together with 3 controls,

with 0.000,001 mg. bovine tubercle bacilli of low virulence. These animals were killed six months later. The immunized animals showed only small local lesions, while one animal had, in addition, 2 small pulmonary tubercles. The controls presented generalized tuberculosis, involving the lungs, liver, spleen and the lymph nodes. The test was repeated with 15 guinea pigs, 5 of which were immunized with 1 mg. vole bacillus injected into the left groin, another 5 similarly with 0.1 mg. Three months later these 10 immunized animals, together with the 5 controls, were injected in the right groin with 0.000,01 mg. human tubercle bacilli. The 5 controls died within three months with generalized tuberculosis. At this time the 5 animals, immunized with the largest vole bacillus dose, were killed and showed only a small local abscess. Among the remaining 5 immunized animals, one died two months after the virulent infection from generalized tuberculosis. The rest were killed one month later. Two of these showed only a local abscess and the rest caseous iliac and portal nodes, as well.

Now followed the larger experiment in which the immunizing effect of vole bacilli was compared with that of the BCG vaccine. A group of 52 guinea pigs was given four weekly subcutaneous injections of 0.5 mg. vole bacilli or a total of 2 mg. Each of another group of 30 animals was given four weekly doses of 7.5 mg. BCG, or a total of 30 mg., which the authors held to be "optimum immunizing dose for guinea pigs." Unfortunately, they lost 19 animals in the vole bacillus group and 8 in the BCG group from a *Pasteurella septica* infection. Five months after the last immunizing dose, half the surviving animals in each group were injected subcutaneously in the left axilla with 0.000,001 mg. bovine tubercle bacilli and the second half with 0.000,001 mg. human tubercle bacilli by the same route. Sixteen control animals were simultaneously injected, half with bovine and the other half with human tubercle bacilli. Wells and Brooke had originally intended "to keep these animals for eighteen months, or as long as they survived, in order to determine the survival time in each group." Because of the war stringencies, this plan was curtailed. The animals were therefore killed only eleven weeks after the virulent infection, except for one animal which died sixteen weeks after infection and 2 which were killed four weeks later. At autopsy all the unvaccinated controls showed extensive tuberculosis. Most of the animals immunized with vole bacillus showed no lesions at all or only a small regressive (?) local abscess. The BCG immunized animals all showed generalized tuberculosis, though less advanced than the controls. Tuberculin tests were made with 1:20 up to 1:10,000 dilution of purified protein derivative three, four, eight and eleven weeks after the virulent infection, in order to determine the highest dilution of tuberculin to which the animals reacted at various times. Eight weeks after infection all the controls and BCG immunized animals reacted with the 1:100 dilution, but only 8 out of 15 animals immunized with the vole bacillus reacted with this dilution. At eleven weeks, 15 out of 16 controls and 3 out of 8 BCG animals reacted with the 1:1,000 tuberculin dilution while none of the vole bacillus animals reacted with this high dilution. Thus, it was apparent that tuberculin sensitivity took longer time to develop in the vole immunized group than in the BCG group.

Another *intra vitam* indication of the greater protection afforded by the vole bacillus against tuberculous infection than BCG vaccination was the slower rate of hypertrophy of the left axillary nodes in the vole bacillus group than in the BCG animals. Thus, six weeks after the virulent infection all controls showed greatly enlarged nodes and 7 out of 8 BCG animals, and 7 out of 15 vole bacillus animals presented tiny palpable nodes. Ten weeks after infection, all controls and BCG animals and only 10 out of 15 vole bacillus animals presented greatly enlarged left axillary lymph nodes.

In summarizing these experimental data, which admittedly are statistically inconclusive, Wells and Brooke nevertheless made the following emphatic conclusion: "Vaccination of guinea pigs with the vole acid-fast bacillus prior to infection with virulent mammalian tubercle bacilli gives a degree of protection which apparently is far greater than has been recorded by other means."

The only other study on the immunizing value of the vole bacillus against tuberculous infection which has come to our notice is that made by Wahlgren, Olin and Widström (6) last year at the State Bacteriological Laboratory at Stockholm. They received a culture of the vole acid-fast bacillus from Wells in 1942 and immediately set about to confirm the work of Wells and Brooke. It should be mentioned at once that their experimental procedure deviated considerably from that of the English investigators. Neither did they heed the implied wish to determine the survival time in each group of animals—a procedure which the contingencies of war interfered with for our English colleagues and which apparently did not arise in neutral Sweden.

Wahlgren and coworkers injected 15 guinea pigs subcutaneously with 1 mg. vole bacilli and the same number of animals with 10 mg. BCG. (It is recalled that Wells and Brooke employed 2 mg. and 30 mg. respectively, of these organisms.) The number of animals was reduced by intercurrent infection to 10 and 14, respectively. Tuberculin tests were done one and three months after immunization. All the animals reacted to the 1:100 dilution of tuberculin one month after inoculation and some animals to the 1:1,000 dilution three months after vaccination. The degree of tuberculin sensitization was apparently identical in both groups of animals. Three months after vaccination all the immunized and 12 unvaccinated guinea pigs were each injected subcutaneously with 0.05 mg. human tubercle bacilli. (Again it should be recalled that Wells and Brooke employed only 0.000,001 mg. bovine or human tubercle bacilli in their test dose.) The control animals began to die sixty-seven days later and 119 days after the virulent infection 9 controls had succumbed with generalized tuberculosis before any of the immunized groups had died. Four animals in the BCG immunized group died between 122 and 150 days after the virulent infection, while none of the vole bacillus group had died up to this time. The surviving animals were killed 153 days after the virulent infection. Autopsies revealed striking differences in the extent of tuberculous disease in the controls and the immunized groups. While the controls showed extensive generalized tuberculosis of the acute type, both the vole bacillus and BCG groups presented a very limited proliferative type of chronic tuberculosis. But by and large the

Swedish workers gathered the impression that the vole bacillus was just as effective as the BCG, if not slightly better, as an immunizing agent against a virulent tuberculous infection, although they had used ten times less vole bacillus than BCG. But their results were much less decisive than those reported by Wells and Brooke. This they surmise is due to their failure to follow the technique of the English workers who made use of four weekly subcutaneous injections with twice as many vole bacilli and thrice as many BCG and who also killed their animals seventy-seven days after the virulent infection. They argue, however, that a prolonged period of observation most likely would make progressive tuberculous changes more apparent in the immunized animals.

On the basis of the aforementioned editorial in the J. A. M. A. (1) which clandestinely came to our notice in November, 1942, we decided to repeat the original study by Wells and Brooke (2) and to fulfill their wish to determine the longevity of each group of vole bacillus and BCG immunized animals superinfected with a virulent tuberculous infection. The German military officials in Norway refused to transmit to Oxford University our request for a culture of the vole acid-fast bacillus. We managed, however, to smuggle a message across to Stockholm in December, 1942 and this was later transmitted to the Sir William Dunn School of Pathology at the Oxford University. On June 17, 1943 we received two Dorset cultures of the vole bacillus, by the kindness of Doctor Wells. Two years later we were able to terminate our first series of experiments on the protective value of the vole bacillus as compared with BCG against tuberculous infection.

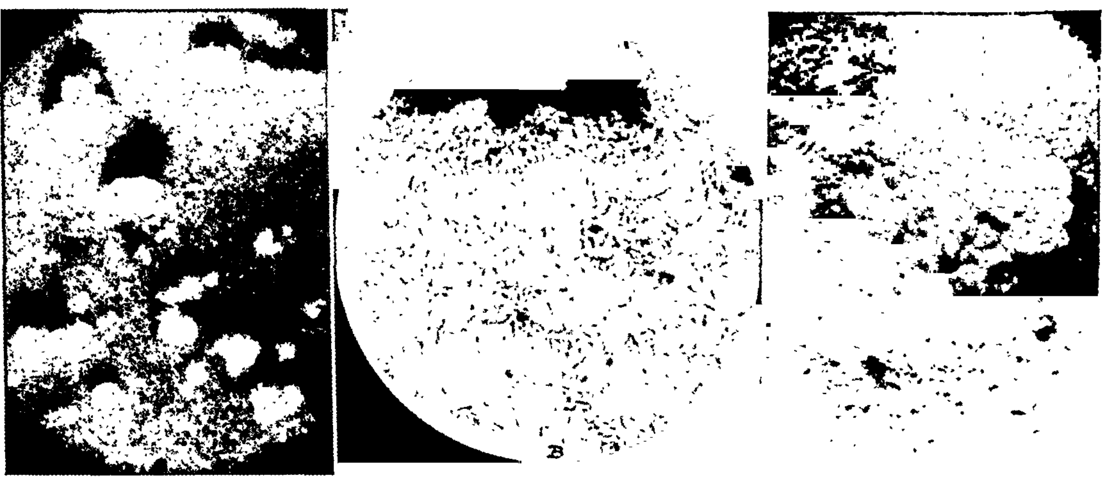
BACTERIOLOGICAL OBSERVATIONS

Cultural characteristics: Attempts to obtain growth of the vole strain in glycerinated solid or liquid media were mainly negative. We failed likewise to obtain any visible growth on ordinary potato or agar enriched with carbohydrates, ascitic fluid, serum, blood, etc. Dorset's egg medium gave the best growth and serves the purpose of propagating the vole strain. On this medium the growth is decidedly dysgonic and becomes visible to the naked eye in form of tiny, creamy white hemispherical colonies in the course of three to four weeks at 37.5°C. No growth takes place at room temperature. The colonies continue to grow into conical and granular shapes, simulating a cauliflower shape (figure 1A). On only one occasion did we obtain good growth of the vole strain on ox-bile potato. In the course of one year at 37.5°C. we observed the initial translucent film grow into the picture seen in figure 1C. But subcultures on ox-bile potato grew exceedingly slowly. The growth on Dorset's egg medium is essentially of smooth appearance and is readily suspended evenly in saline.

The vole bacillus is gram-positive and stains with the Ziehl-Neelsen method. The bacilli are slender, highly irregular in shape, varying between straight rods, spirals, sickles and commas. The rods and spirals are much longer than ordinary human tubercle bacilli. They are finely granular and show marked vacuolation. The characteristic "shepherd's crook," described by Griffith (4), is readily seen in direct smears of caseous material, but not often in the culture. No branched forms have been seen. (Figures 1A, B and C.)

Virulence tests: Six white mice were injected intraperitoneally with 0.5 mg. vole bacilli from a six-weeks' growth on Dorset's medium. The mice died respectively 41, 51, 67, 306, 311 and 314 days later. None of them presented any generalized tuberculous disease. But all showed transparent nodules in the omentum and occasionally in the liver and lungs. Numerous acid-fast rods could be demonstrated in these nodules which histologically were made up of epithelioid cells. Cultures were obtained on Dorset's medium in the first 3 animals, but were sterile in the last 3 animals.

Two guinea pigs were injected intracranially with 1.0 mg. vole bacilli. They succumbed thirteen and seventeen days later from a subacute meningitis resembling tuberculosis. Tiny gray nodules were seen in the meninges, brain, lungs, liver and spleen. Almost all the lymph nodes showed slight hyperplasia.



A B C

Fig. 1. (A) Colonies of vole bacillus on Dorset's medium after eight weeks' incubation. (B) Vole bacilli from Dorset's medium. Ziehl-Neelsen stain. (C) Spreading colonies of vole bacillus after one year's growth on ox-bile potato.

Enormous numbers of acid-fast rods were found in these nodules and cultures produced growth.

Two guinea pigs were injected intravenously with 1 mg. vole bacilli. They died seventeen and thirty-four days later and showed acute miliary tuberculous lesions in the lungs, liver, spleen and kidneys. They both showed marked glandular hyperplasia. Again, we observed a characteristic abundance of acid-fast rods in the lesions and rich growths on Dorset's medium.

Two guinea pigs each were injected intraperitoneally with 1.0 mg. vole bacilli. They died sixteen and thirty-five days later from generalized disease resembling acute disseminated tuberculosis. The omentum was rolled up into a sausage-like caseous mass. Purulent deposits were noted on the mesenteries and in the lumbo-sacral regions. The spleen was enlarged and deeply red, showing milky spots rich in acid-fast bacilli. The lymph nodes were generally enlarged, especially in the abdominal cavity. An abundance of acid-fast rods were found in all the viscera and cultures yielded growths. Repeating the intraperitoneal

injection with 0.1 and 0.01 mg. on 4 guinea pigs, the animals survived much longer and died fifty-six and seventy-eight days after the 0.1 mg. dose and seventy-two and ninety-five days after the 0.01 mg. dose. The omentum reacted as it did with the larger dose and presented caseous as well as transparent nodules. But the generalized disease was much milder. The number of acid-fast rods was proportionally fewer in the animals which died ninety-five days after inoculation, indicating regression of the disease.

Six guinea pigs each were injected subcutaneously with 5.0 mg. vole bacilli in the left leg. The adjacent inguinal lymph nodes became greatly hypertrophied in the course of the next two weeks. The local abscess ulcerated in every animal and the lesions healed completely. The inguinal nodes remained hypertrophied during several months and gradually became smaller. These 6 animals survived over six months when they were killed. Except for slightly hypertrophied left inguinal and iliac nodes, we found nothing abnormal. Occasional acid-fast rods were found after much search in some of the nodes, but the cultures yielded no colonies.

These findings are confirmatory of the results obtained by Griffith (4) that the vole bacillus injected intraperitoneally, intravenously and intracranially in relatively larger doses may cause death from generalized disease resembling tuberculosis both macroscopically and microscopically. Injected intraperitoneally and subcutaneously in smaller doses, the vole bacillus causes only local lesions which regress and heal completely. Our preliminary studies demonstrated likewise that the intracutaneous and percutaneous inoculations with the vole bacillus produce a strong tuberculin allergy and skin lesions which shortly suppurate and subsequently heal completely.

INTRACUTANEOUS IMMUNIZATION OF GUINEA PIGS WITH THE VOLE BACILLUS AND BCG

Animals used: Forty-eight normal albino guinea pigs, which failed to react with 10 mg. Old Tuberculin intracutaneously, were divided into four equal groups, each containing 6 male and 6 female animals. Groups I and II were immunized with the vole strain of acid-fast bacilli, group III with BCG and group IV was not immunized, but was retained as controls for the subsequent virulent tuberculous infection.

Preparatory to immunization, complete differential leucocyte counts were done on all animals on three occasions with weekly intervals. These counts were continued with monthly intervals until all the animals in groups II, III and IV had died spontaneously in the course of twenty months after infection. These hematological data will be published separately.

Our animals were carefully selected from a strain which had proved unusually resistant to intercurrent infection—the bane of every tuberculosis immunity study of long duration. The average body weight for each group of animals was nearly identical when the experiment began, namely, 348 g. in group I, 354 g. in group II, 317 g. in group III and 310 g. in group IV.

The housing and feeding conditions were identical for all the animal groups during the entire experiment.

Immunization: The 24 guinea pigs in groups I and II were each injected intracutaneously along the side of the body with 0.5 mg. vole bacilli on four occasions with weekly intervals, receiving a total of 2.0 mg. vole bacilli, exactly weighed out from a six-weeks' growth on Dorset's medium. The 12 animals in group III were similarly injected with a total of 30.0 mg. BCG, exactly weighed out from a three weeks old Sauton culture. It should be noted that these doses are identical with those employed by Wells and Brooke (2).

Post-immunization tuberculin reactions: The post-immunization skin reactions were equally intense in the vole bacillus and the BCG groups. It was quite apparent that after each succeeding inoculation with vole bacilli and BCG, induration, suppuration and sloughing of the overlying skin became accelerated, due to increasing degrees of allergy.

One month after the last immunizing dose or two months after the beginning of immunization, we made intracutaneous injections with 1.0 mg. (1:100), 0.1 mg. (1:1,000) and 0.01 mg. (1:10,000) dilutions of purified protein derivative tuberculin, contained in 0.1 ml. saline. Readings of the reactions were made both at twenty-four and forty-eight hours. The induration was measured with a pair of calipers. The approximate volume of induration was estimated by multiplying half the thickness of the folded skin by the two diagonal diameters of the palpable indurated area. The central necrosis was expressed in mm^2 by multiplying the breadth and width of necrotized skin. Table 1 presents these data.

Thus it is apparent that the four weekly intracutaneous injections with a total of 30 mg. BCG are capable of rendering guinea pigs more tuberculin sensitive than similar injections with a total of 2.0 mg. vole bacilli.

Virulent tuberculosis inoculation: Two months after the immunization with the vole bacillus and BCG, we retained group I (12 animals) as controls on possible pathological changes caused by the vole bacillus alone. This group is henceforth designated as group I—*vole bacillus normal controls.* At the same time each of the 12 animals in group II—*vole bacillus immunized,* and the 12 animals in group III—*BCG immunized,* together with the 12 non-immunized animals in group IV—*control tuberculous infection,* were inoculated subcutaneously in the left leg with 0.000,001 mg. virulent human tubercle bacilli. Seeded out on Löwenstein's egg medium, this dose gave rise to 48 colonies of acid-fast bacilli. We may infer, therefore, that each animal was infected with approximately 50 viable tubercle bacilli. In previous virulence tests with this dose of bovine bacillus, guinea pigs died approximately 200 days later with generalized tuberculosis.

Six weeks after the virulent tuberculous inoculation, all the animals were retested intracutaneously with 10 mg. purified protein derivative tuberculin. Readings forty-eight hours later gave the following average measures of induration and central necrosis respectively: group I—1,945 mm^3 and 36.7 mm^2; group II—2,327 mm^3 and 94.5 mm^2; group III—2,541 mm^3 and 91.4 mm^2; group IV—3,170 mm^3 and 171.5 mm^2. These data demonstrate that the progress of tuberculin sensitization is considerably slowed down in guinea pigs immunized with the vole bacillus or BCG.

Another proof of this statement are the data on the weekly palpation of the left inguinal lymph nodes at the site of the virulent tuberculous inoculation. Six weeks after the virulent inoculation, these lymph nodes were already markedly hypertrophied and of hard consistency in 10 out of 12 animals in group IV, while nothing unusual was noted in the immunized groups. After three months, these nodes were greatly enlarged and of soft consistency in all animals of group IV, while they were only slightly palpable and still of hard consistency in 5 out of 12 animals of group II and in 4 out of 12 animals in group III. After six months, suppuration was noted in most of the group IV animals, while the left inguinal nodes were markedly enlarged but still of hard consistency in 8 out of 12 group II animals and in 7 out of 12 group III animals. After twelve months the nodes were hugely hypertrophied in 8 out of 10 surviving group II animals and in 7 out of 10 surviving group III animals. But suppuration was not encountered in any of these animals. Nineteen months after the virulent inoculation the left inguinal nodes were greatly enlarged, of semi-hard consistency but not suppurating in one

TABLE 1

Tuberculin skin sensitivity one month after immunization with the vole bacillus and BCG

ANIMAL GROUP	READING HOURS	DILUTIONS OF PPD TUBERCULIN					
		1 mg. 1:100		0.1 mg. 1:1,000		0.01 mg. 1:10,000	
		Induration mm²	Central necrosis mm²	Induration mm²	Central necrosis mm²	Induration mm²	Central necrosis mm²
I—Vole bacillus	24	1,309	21.2	395	0	102	0
I—Vole bacillus	48	1,483	46.3	323	0	42	0
II—Vole bacillus	24	1,267	19.5	329	0	98	0
II—Vole bacillus	48	1,420	51.6	253	0	40	0
III—BCG	24	1,747	28.0	519	0	100	0
III—BCG	48	1,778	74.5	372	0	47	0

animal surviving in group II and in the 3 surviving group III animals. From these data we may infer that the rate of lymph node involvement was slightly more rapid in the animals immunized with the vole bacillus than in the animals immunized with BCG. No abnormal changes in the size of the inguinal nodes were observed during this time in the animals in group I.

Survival time: Chart 1 shows the survival time of the animals in groups II, III and IV. We note that the animals in group IV (control tuberculous infection) began to die 159 days after the virulent inoculation and that the last animal in this group died 219 days after inoculation. The average survival time in this group is 192 days with a standard deviation of 20.6 days. In group II (vole bacillus immunized) the first animal died 303 days after the virulent inoculation and the last animal succumbed 613 days after the tuberculous inoculation. The average survival time in this group is 403 days with a standard deviation of 64.7 days. In group III (BCG immunized) the first animal died 288 days and the last animal 632 days after the virulent tuberculous inoculation.

The average survival time in this group is 429 days with a standard deviation of 86.3 days.

By statistical analysis according to Fisher's (7) method for comparison of two comparable means, we find that the difference in survival time between group IV and group II is of undisputed significance ($t = 7.989$ and $P < 0.001$) and likewise the difference between group IV and group III ($t = 6.671$ and $P < 0.001$). But by comparing the survival time difference between groups II and III we find that they both belong to the same population and hence do not differ significantly from each other.

The data on survival time decide the issue at stake in these experiments, namely to ascertain the verity in the emphatic statement made by Wells and

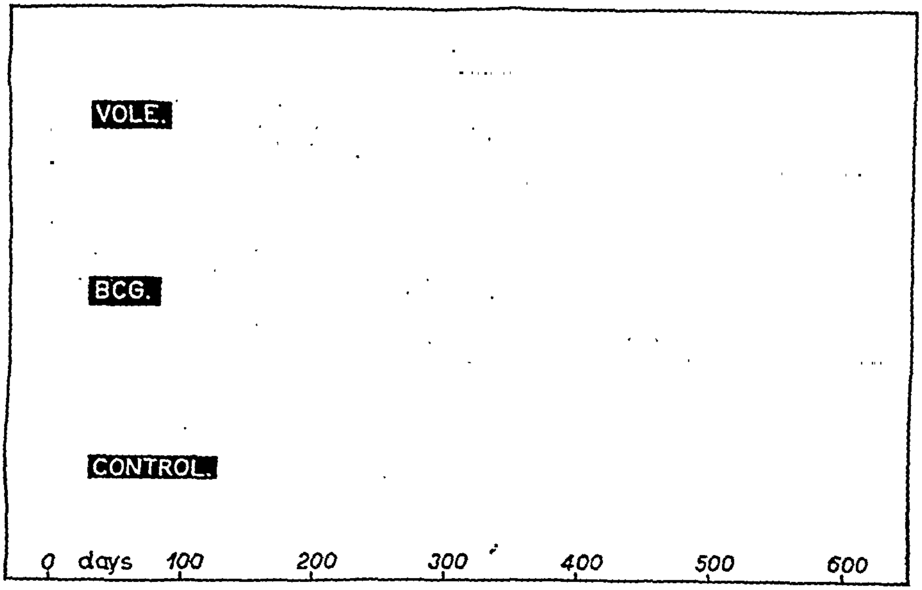


CHART 1. Survival time of vole bacillus immunized group II, BCG immunized group III and control tuberculous infection group IV animals (12 animals in each group).

Brooke (2) that, "Vaccination of guinea pigs with the vole acid-fast bacillus prior to infection with virulent mammalian tubercle bacilli gives a degree of protection which apparently is far greater than has been recorded by other means." This statement was not based on the survival time of the animals immunized by the vole bacillus or BCG, but on the pathological material from animals killed eleven weeks after the virulent inoculation. By carrying out the expressed wish of our English colleagues "to leave all the animals for 18 months, or as long as they survived, to determine the survival time in each group," we find that the effect of vaccination of guinea pigs with the vole acid-fast bacillus and BCG on a subsequent tuberculous infection is equally potent and of a very high protective order.

Quantitative assessment of tuberculous hyperplasia: With few exceptions, tu-

berculosis was severe in all the immunized and non-immunized guinea pigs and was typical of infection with virulent bovine tubercle bacilli. The effect of immunization with either the vole bacillus or BCG was simply to delay the progress of tuberculosis. By making use of the macroscopic scoring of tuberculous involvement designed by Petroff and Steenken (8) we found that the *vole bacillus immunized* group presented 2 animals with ++, 5 animals with +++ and ++++ tuberculous involvement, respectively. The *BCG immunized* group had 2 animals with + and ++, respectively, 3 with +++ and 7 with ++++ tuberculous involvement. In the *control tuberculous infection* group each of the animals presented ++++ generalized tuberculosis. From these scorings it becomes apparent that, when the immunized animals are allowed to die spontaneously following the virulent tuberculous infection, they present nearly the same macroscopic picture as the non-immunized tuberculous controls. In subsequent experimental work on the protective value of the vole bacillus on a virulent tuberculous infection, we terminated the experiment when all the non-immunized tuberculous controls had succumbed with generalized tuberculosis and only one of the vole bacillus immunized guinea pigs had died spontaneously. This work will be published shortly.

In order to ascertain whether or not quantitative differences obtain in the tuberculous hyperplasia in the viscera of the vole bacillus and BCG immunized animals and the non-immunized tuberculous controls, we will present the exact weights and volumes of the spleen, liver, lungs, individual and total lymph nodes and some of these data converted into the more exact percentage of the animal's body weight. Our quantitative procedure is the same as described in our previous publications (9).

Volume of lymph nodes: Table 2 presents the volumetric data on 15 different lymph nodes as well as the weight of these pooled (total) nodes. At the right of the volume we have placed the statistical analysis of these data in terms of the quotient of probable error (t) and the degree of significance (P). Thus we compare the differences between the glandular volumes in groups II and IV, III and IV and finally II and III. The remarkable feature in these comparisons is that the same sets of nodes attaining significant differences from those in the group of control tuberculous infection (IV) figure in both the immunized groups, namely the following nodes: right knee, right superior inguinal, right deep inguinal, left and right cervical nodes. We would have expected to find that the lymph nodes in the left lower extremity, where the virulent inoculation was made, would present significant deviations in both immunized groups from those in the control group. But in spite of the fact that the average volume of the nodes from the immunized animals is smaller than that of the corresponding nodes in the control animals, they do not attain significant deviations because of extreme variations within the group. But the pooled (total) nodes mirror more clearly the true volumetric differences between the lymph nodes from the non-immunized tuberculous control animals and those from either the vole bacillus immunized or BCG immunized animals. In both instances the differences have absolute statistical significance in favor of immunization. But the degree of protection

is equally divided between the vole bacillus and the BCG immunized groups, an efficiency of 37.5 per cent in both groups.

By comparing the differences in lymph node volumes in the vole bacillus (II) and the BCG (III) groups in the columns at the extreme right in the table, we find that they belong to the same population with but one exception, namely

TABLE 2

Tuberculous hyperplasia in lymph nodes from vole bacillus immunized (II), BCG immunized (III) and control tuberculous infection (IV) animals

Statistical analyses of volume (in ml.) of nodes from 12 animals in each group

LYMPH NODES	VOLE BACILLUS IMMUNE (II)			BCG IMMUNE (III)			CONTROL (IV)	PROBABILITY	
	Volume in ml.	Probability II vs IV		Volume in ml.	Probability III vs IV		Volume in ml.	II vs III	
		t	P		t	P		t	P
Knee left	0.04	2.450	0.03	0.09	1.225	0.25	0.16	1.289	0.02
Knee right	0.04	3.418	*<0.01*	0.02	5.292	*<0.01*	0.10	1.580	0.15
Sup. inguinal left	0.52	2.102	0.06	0.68	1.717	0.10	1.55	0.674	0.50
Sup. inguinal right	0.21	4.337	*<0.01*	0.20	5.052	*<0.01*	0.53	0.175	0.85
Deep inguinal left	0.22	0.544	0.60	0.10	1.367	0.20	0.34	0.816	0.40
Deep inguinal right	0.05	3.026	*<0.01*	0.06	2.922	*<0.01*	0.26	0.407	0.65
Femoral left	0.29	1.735	0.10	0.28	2.004	0.07	0.46	0.106	0.90
Femoral right	0.32	1.339	0.20	0.31	1.445	0.15	0.44	0.091	0.90
Axilla left	0.19	1.441	0.20	0.21	1.052	0.30	0.28	0.314	0.75
Axilla right	0.15	1.776	0.10	0.20	0.897	0.40	0.24	1.289	0.25
Trach. bronch. left	1.21	0.217	0.80	1.15	0.044	0.90	1.16	0.223	0.85
Trach. bronch. right	0.98	0.116	0.90	1.07	0.406	0.65	1.00	0.441	0.65
Cervical left	0.14	4.496	*<0.01*	0.25	2.813	*<0.01*	0.52	2.173	0.05
Cervical right	0.11	4.290	*<0.01*	0.25	2.832	*<0.01*	0.59	3.112	*<0.01*
Periportal	1.97	0.328	0.75	1.01	1.764	0.10	1.55	1.110	0.30
Total lymph nodes in grams	8.50	3.121	*<0.01*	7.71	3.974	*<0.01*	15.0	0.477	0.65
Efficiencies in per cent			37.5			37.5			6.2

N.B. In Fisher's 1938 tables for distribution of t (quotient expressing the deviation as a multiple of its probable error), we observe that a $P \leqq 0.01$ (probability that the observed mean deviation bearing this or smaller values cannot have occurred by chance alone) requires that $t \geqq 2.819$ when each group contains 12 animals or samples. Every difference having *absolute significance* is italicized in tables 2 and 3.

the right cervical node which is significantly smaller in the vole bacillus immunized group.

In short, we may state that, on the basis of volumetric data on lymph nodes, vaccination with either the vole bacillus or BCG produces a significant deterring action on the spread of tuberculous disease throughout the lymphatic system. But the protective action of the vole bacillus against a virulent tuberculous infection is apparently of the same degree as that which is produced by BCG.

Chart 2 clearly depicts the differences in lymph node volumes in the four groups of animals reported on in this paper.

Volumes and weights of spleen, liver and lungs: Table 3 presents the data on tuberculous hyperplasia in the spleen, liver and lungs. In guinea pig tuberculosis one attaches the greatest importance to the changes in the spleen, which in this

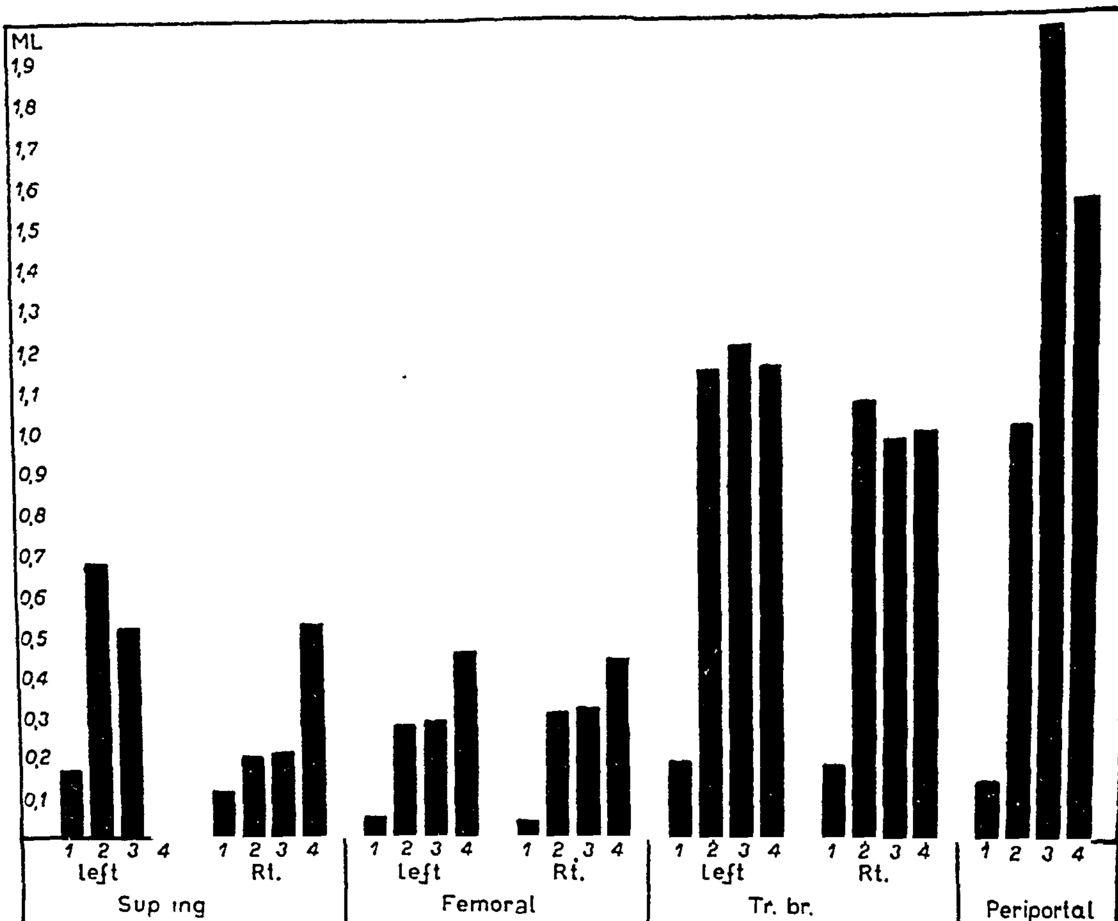


CHART 2. Average volume of lymph nodes from (I) normal vole bacillus immunized, (II) vole bacillus immunized and tuberculous infection, (III) BCG immunized and tuberculous infection and (IV) control tuberculous infection animals.

Volume of lymph nodes: 1. Vole normal group. 2. BCG + tbc group. 3. Vole + tbc group. 4. Control tbc.

species is the most vulnerable organ in tuberculous disease. On the basis of the actual weights of the spleen, we observe that the average weight was 7.2 g. in group IV, while it was 2.7 g. in group II and 3.5 g. in group III. Both these latter weights differed significantly from the weight of the spleens in the control group. We failed to observe any other significant deviations between the three groups in regard to weight or volume of the liver and lungs. Individual varia-

tions were extreme in all groups and account for the apparent similarities of liver and lung weights and volumes within the immunized and non-immunized animal groups. A truer picture of tuberculous hyperplasia in the spleen, liver and lungs is obtained by expressing the weights of these organs in percentage of the animal's body weight which may vary considerably from animal to animal. By glancing at the lower part of table 3, we observe that on this basis we obtain significant deviations in the data on the spleen, liver and lungs in both the vole bacillus and BCG immunized groups from that in the non-immunized control animals. But, even as with the volumetric data on the lymph nodes, we again find it impossible to discern any advantage of the vole bacillus over BCG as a protection against a virulent tuberculous infection. They are both capable of

TABLE 3

Tuberculous hyperplasia in spleen, liver and lungs

Statistical analyses of weights, volumes and weights expressed in percentage of body weight —12 animals in each group

ORGANS	VOLE BACILLUS IMMUNE (II)			BCG IMMUNE (III)			CONTROL (IV)	PROBABILITY	
	Average	Probability II vs IV		Average	Probability III vs IV		Average	II vs III	
		t	*P*		*t*	*P*		*t*	*P*
Spleen g.	2.7	4.594	<*0.01*	3.5	4.028	<*0.01*	7.2	0.889	0.40
Liver g.	37.0	1.960	0.08	38.0	1.396	0.20	42.6	0.370	0.75
Liver ml.	36.2	1.392	0.20	37.4	1.475	0.20	41.4	0.291	0.80
Lungs g.	14.6	2.506	0.03	16.0	1.499	0.20	19.0	0.659	0.50
Lungs ml.	17.5	1.886	0.09	18.5	1.350	0.20	21.2	0.438	0.65
Weights expressed in percentage of body weight									
Spleen per cent.	0.50	4.856	<*0.01*	0.62	4.410	<*0.01*	1.65	0.073	0.90
Liver per cent.	6.71	4.224	<*0.01*	7.05	3.768	<*0.01*	9.22	0.453	0.65
Lungs per cent.	2.82	3.329	<*0.01*	2.81	3.464	<*0.01*	4.23	0.000	0.90
Efficiency per cent.			50			50			0

producing a significant mechanical barrier to the inevitable progression of tuberculous disease. But this protection is anything but absolute.

In chart 3 we have contrasted the weights of the spleen, liver, lungs and total lymph nodes, expressed in percentage of the animal's body weight, for the vole bacillus and BCG immunized groups II and III, the tuberculous controls in group IV as well as for the normal group I which measures the virulence of the vole bacillus alone.

In regard to the animals in group I which were, at four weekly intervals, intracutaneously injected with a total of 2.0 mg. vole bacillus in order to study the pathological changes produced in the guinea pig, we observed the following: Four of these 12 animals died spontaneously 211 (1), 214 (2) and 217 (1) days after inoculation. They were in the same cage and each died from a pneumo-

coccic croupous pneumonia. No trace of tuberculous disease was found in any of these animals and cultures of the left axillary and inguinal nodes remained

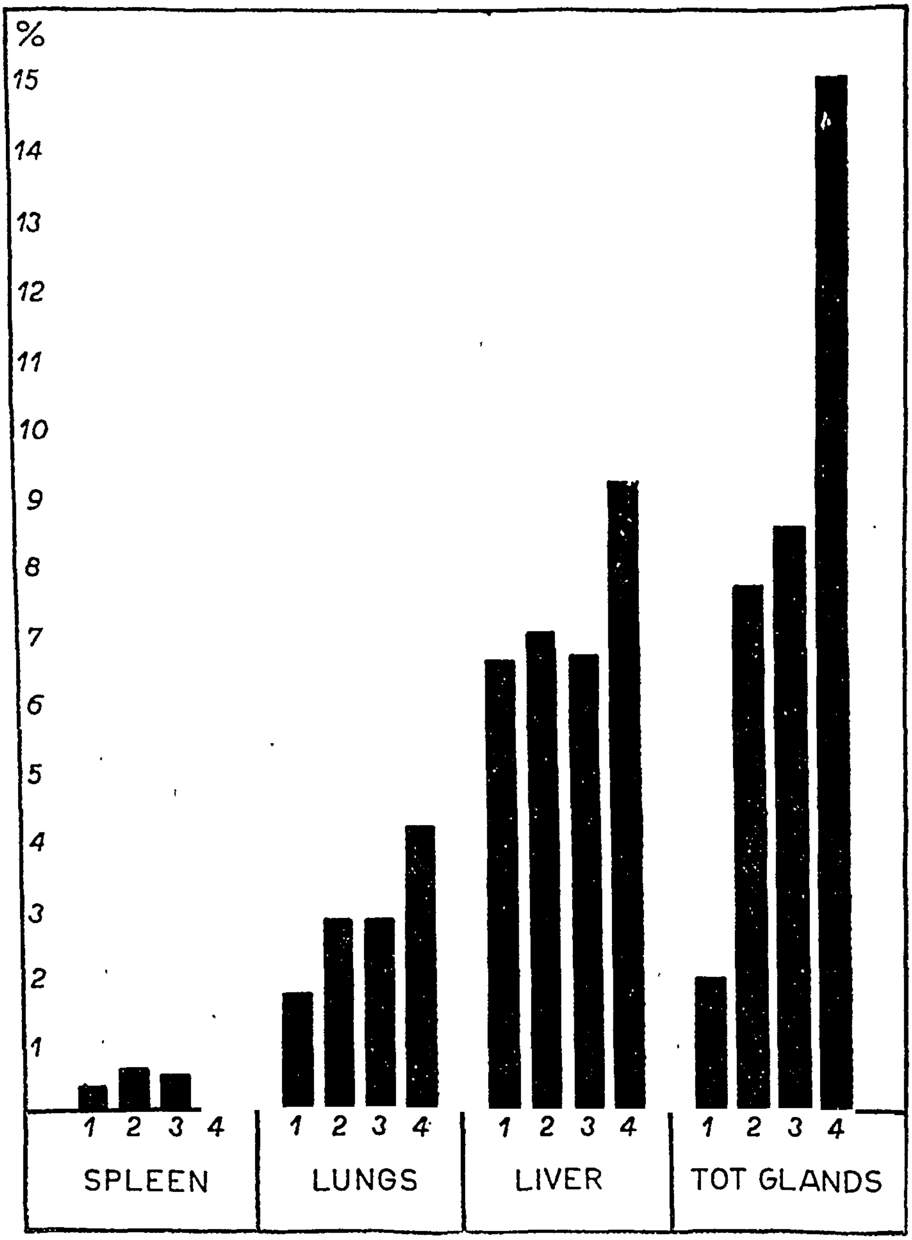


CHART 3. Average weights of liver, lungs, spleen and total lymph nodes, expressed as per cent of body weight.

Per cent of body weight: 1. Vole normal group. 2. BCG + tbc group. 3. Vole + tbc group. 4. Control tbc group.

sterile. The vole bacilli had apparently died out within seven months. The remaining 8 animals in this group were killed 613 days after the inoculation with

vole bacilli; these, likewise, showed no tuberculous changes and the cultures of the left axillary and inguinal nodes were sterile. We have tabulated the volumes and weights of various lymph nodes and internal organs in this group and have compared these data statistically with those of groups II, III and IV. In nearly every instance these normal organs differ significantly from their corresponding organs in the vole bacillus immunized and subsequently tuberculosis infected group II animals. We are compelled, therefore, to conclude that the hyperplastic changes observed in the viscera and lymph nodes in group II are produced by the bovine tubercle bacilli and not by the vole bacillus. This long passage of vole bacilli in the guinea pig confirms the opinion expressed by Griffith (4) that "the lesions . . . produced by small doses intraperitoneally or large doses subcutaneously heal completely, the bacilli die out."

Thus, we have carried out the wish of Wells and Brooke (2) "to leave all the animals for 18 months, or as long as they survived, to determine the survival time in each group." In the following studies, which are terminated and are now being assembled, we shall present the hematological data on the animal groups discussed in this paper; the protective value of percutaneous (multiple puncture) vaccination of guinea pigs with the vole bacillus on a subsequent tuberculous infection; preliminary multiple puncture vole bacillus vaccination of man; and finally biological differences between avian, bovine, human tubercle bacilli, the vole bacillus and *M. paratuberculosis* elicited by means of the Koch phenomenon.

SUMARY

Intracutaneous vaccination of guinea pigs with the vole acid-fast bacillus (Wells), prior to infection with virulent human tubercle bacilli, gives a high degree of protection which is equal to, but not greater than that produced by vaccination with BCG.

SUMARIO

La vacunacíón intracutánea de los cobayos con el bacilo ácidorresistente del ratón campestre (Wells) antes de la infección con bacilos tuberculosos humanos virulentos, facilita una protección elevada que es igual a la producida por la vacuna BCG, pero no mayor que ésta.

The author is greatly indebted to his assistant, Dr. Halfdan Schjelderup, Dr. Einar Berle and Mr. Sigbjörn Aamodt, for invaluable technical and statistical assistance.

REFERENCES

(1) Editorial, J. A. M. A., 1941, *116*, 509.
(2) Wells, A. Q., and Brooke, W. S.: Brit. J. Exper. Path., 1940, ,*21* 104.
(3) Wells, A. Q.: Lancet, 1937, *1*, 1221.
(4) Griffith, A. Stanley: J. Hyg., 1942, *42*, 527; 1939, *39*, 154, 244; 1941, *41*, 260.
(5) Griffith, A. Stanley, and Dalling, T.: J. Hyg., 1940, *40*, 673.
(6). Wahlgren, F., Olin, G., and Widström, G.: Nordisk Medicin (Stockholm), 1944, *22*, 943.
(7) Fisher, R. A., and Yates, F.: Statistical Tables, Oliver and Boyd, London, 1938, p. 26.
(8) Petroff, S. A., and Steenken, W.: J. Immunol. 1930, *19*, 79.
(9) Birkhaug, K.: Acta tuberc. Scandinav., 1939, *13*, 163, 221; 1940, Suppl. V, pp. 1—60; Acta med. Scandinav., 1942, *112*, 393.

VOLE BACILLUS

Susceptibility of South African Wild Rodents to the Vole Strain of Acid-fast Bacillus and to Other Acid-fast Bacilli

Preliminary Report

E. GRASSET,[1] J. F. MURRAY[1] AND D. H. S. DAVIS[2]

INTRODUCTION

Isolation of an acid-fast bacillus from naturally infected voles in England was first reported by Wells (1937). Further contributions to a knowledge of this organism were made by a number of workers and are summarized in an article on the subject by Brooke and Day (1944), which gives a complete bibliography.

The present work was undertaken to study some of the biological properties of the organism and to ascertain the susceptibility of South African wild rodents.

A culture (D/15) was received by us in August, 1941, thanks to the courtesy of Dr. A. Q. Wells. Following his instructions, subcultures were made on Dorset's medium without glycerin. The first subculture was extremely slow in establishing itself. After three months' incubation at 37°C. minute colonies were observed. They reached 2 to 3 mm. diameter after five months' incubation. Microscopic examination showed acid-fast bacilli frequently curved and S-shaped as described by Brooke (1941) and Griffith (1942). Since 1941 subcultures have been made on Dorset's medium without and with glycerin (1 per cent). Development of colonies became somewhat more rapid but remained slow in growth as compared with human and bovine strains of the tubercle bacillus. Isolated colonies of vole bacillus on this medium continued to develop during eight to ten months' incubation, reaching 2 to 4 mm. diameter with raised centre, waxy appearance and containing elements of different degrees of acid-fastness and rare branching forms.

The susceptibility of the following South African wild rodents was investigated and compared with that of guinea pigs and rabbits. A high tolerance of guinea pigs and rabbits to the vole bacillus has been shown by Brooke (1941) and Griffith (1942).

Multimammate mouse (*Mastomys coucha-Muridae-Murinae*)
Cape gerbil (*Tatera afra-Muridae-Gerbillinae*)
Transvaal gerbil (*Tatera brantsii-Muridae-Gerbillinae*)
White footed rat (*Mystromys albicaudatus-Muridae-Cricetinae*)

The gerbils were healthy adult trapped specimens which were kept in the laboratory for a few days before use. The *Mastomys* and *Mystromys* were laboratory-bred animals. All these animals have been used here under laboratory conditions for some years. The *Mastomys* is extensively employed by us as a test animal in experimental plague work. The gerbils are utilized in plague

[1] South African Institute for Medical Research, Johannesburg, South Africa.
[2] Union Health Department.

studies and also in the production of typhus vaccine. *Mystromys* has been used by us experimentally in leprosy, plague and typhus work. At no time, in the thousands of these animals examined, have we observed lesions in any way resembling those produced by the vole acid-fast bacillus in this investigation.

I

Pathological and Histological Data

(J. F. Murray)

A. TATERA AFRA AND TATERA BRANTSII

As no experimental or histological difference has been observed in the vole bacillus infections of *T. afra* and *T. brantsii* these animals have, for the purposes of this report, been grouped together.

Group I: All inoculations in the initial group were intraperitoneal. The inoculum was suspended in physiological saline by grinding with steel balls in a hard glass tube after weighing the wet growth obtained from a three-month culture on Dorset's medium without glycerin.

Five animals were inoculated with 0.1 mg., 17 with 0.01 mg. and 11 with 0.0001 mg. By the thirty-ninth day 17 animals had died of intercurrent disease showing no macroscopic evidence of vole bacillus infection (table 1). Spleen smears were made from each animal shortly after death. In 2 animals, on the nineteenth and twentieth days after inoculation with 0.01 mg., scanty acid-fast organisms were found in the spleen smears. Sections of the spleen, however, showed no significant pathological change and no acid-fast bacilli could be found in Ziehl-Neelsen preparations. The animal dying on the thirty-ninth day after inoculation with 0.01 mg. also showed scanty acid-fast bacilli in a smear of splenic tissue though there was no macroscopic evidence of infection. Section of the spleen showed minute aggregations of epithelioid cells in the centre of the Malpighian corpuscles. In suitably stained preparations acid-fast bacilli were found in these foci of epithelioid cells. An animal dying on the ninety-third day after inoculation with 0.01 mg. showed such marked postmortem changes that the histological preparations were useless, though numerous acid-fast bacilli were found in spleen smears. Two animals which died on the 130th day after inoculation with 0.01 mg. and 0.1 mg., respectively, showed no macroscopic evidence of infection but on section the spleen showed lesions in the Malpighian corpuscles. The lesions (which are described in detail later) were typical of vole bacillus infection. On being suitably stained they showed numerous acid-fast organisms. The animals which died or were killed after the 218th day showed gross macroscopic lesions which are described later.

Group II: The second group consisted of 21 animals. Six were fed on the organs (spleen, liver and lungs) of 3 animals from group I which, when killed, showed gross macroscopic lesions. Four of the animals died too early to show any lesions (table 1) but the remaining 2, at death on the 317th and 322nd days, showed gross evidence of vole bacillus infection. The nature of the lesions in these orally infected animals will be discussed later.

Subcutaneous and intraperitoneal inoculation of 15 animals with saline suspensions of portions of the same infected organs were also successful in transmitting the infection (table 1).

From these two groups of gerbils it appears that very shortly after intraperitoneal inoculation the bacillus can sometimes be found in spleen smears but no definite histo-pathological lesions were observed before the thirty-ninth day and the earliest definite macroscopic lesions were found on the 108th day after subcutaneous inoculation (table 1).

B. MACROSCOPIC APPEARANCE OF TATERA DYING WITH VOLE BACILLUS INFECTION

Subcutaneous inoculation: Animals inoculated subcutaneously in the groin sometimes showed a local caseous lesion with involvement of the regional lymph

TABLE 1

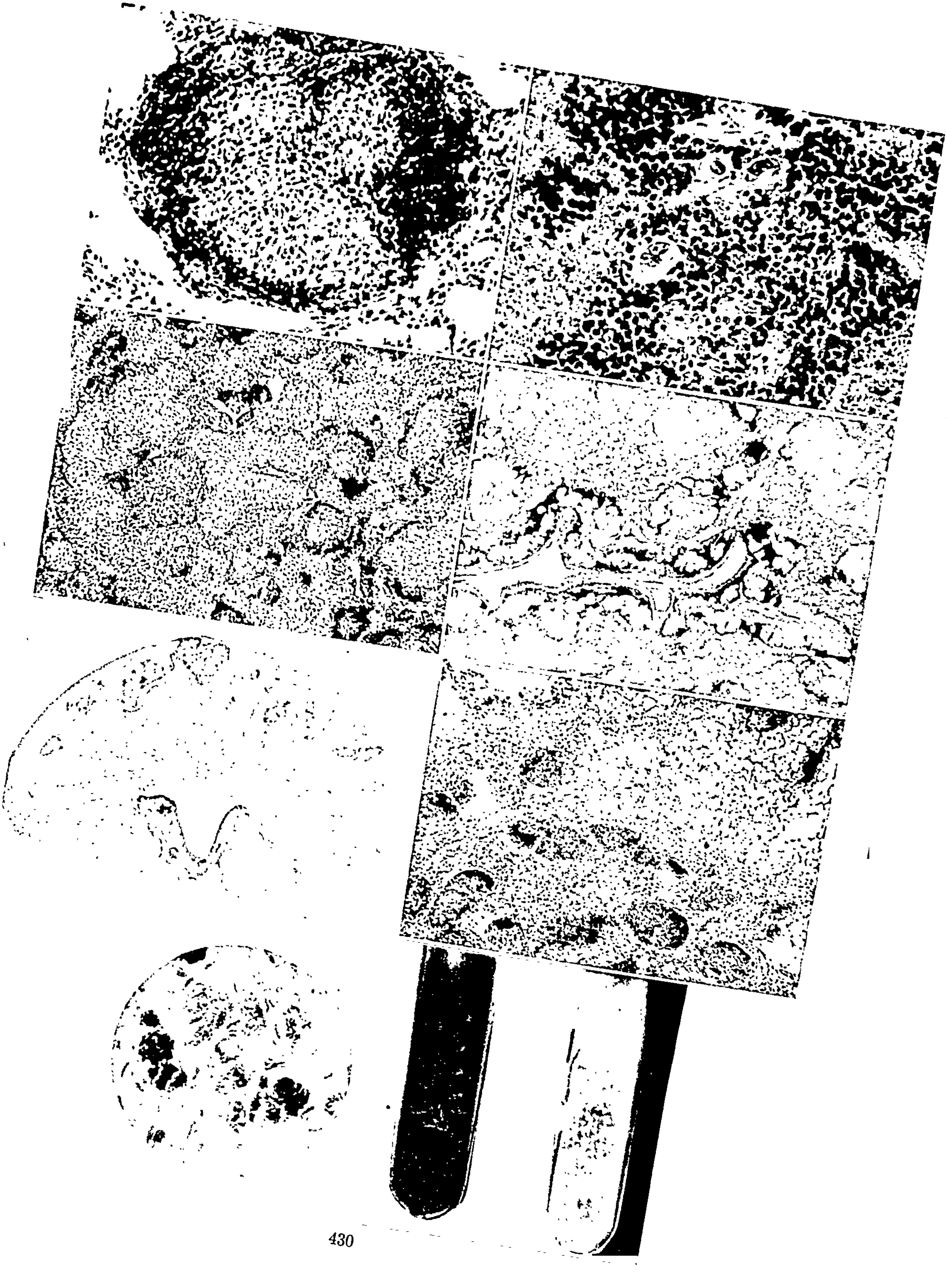
Tatera afra and Tatera brantsii: Days of life after inoculation with vole bacillus

		POSITIVE MACROSCOPICALLY		NEGATIVE MACROSCOPICALLY, POSITIVE MICROSCOPICALLY	NEGATIVE MACROSCOPICALLY AND MICROSCOPICALLY
		Died	Killed	Died	Died
Group I	0.1 mg. culture intraperitoneally	218	230, 247	130	8
	0.01 mg. culture intraperitoneally	221, 222	230, 230, 230, 247	39, 93, 130	13, 16, 17, 18, 19, 19*, 20*, 21
	0.0001 mg culture intraperitoneally	297, 299, 420	247		8, 12, 15, 17, 19, 24, 32
Group II	Infected organs, oral passage	317, 322			2, 5, 45, 153
	Infected organs, saline suspension subcutaneously	108, 115, 140, 165, 209, 306, 323, 338		66	1, 2, 51
	Infected organs, saline suspension intraperitoneally			112	3†, 76

* Scanty acid-fast bacilli found in spleen smear.
† Scanty acid-fast bacilli found in scraping of peritoneum.

nodes. In most instances, however, no evidence of a local lesion was found, the postmortem appearances then being indistinguishable from those following intraperitoneal inoculation. No significant difference was observed in the visceral lesions of animals inoculated subcutaneously and those inoculated intraperitoneally.

Intraperitoneal inoculation: Apart from the local lesion in animals which have been inoculated subcutaneously, the first macroscopic evidence of infection in animals infected by any route is splenomegaly. The spleen is dark purple in color, soft and congested but no tubercles are visible at this stage. When the disease is more advanced it takes the form, macroscopically, of minute yellow tubercles in the spleen. At a later stage the tubercles are found in other organs, notably the liver, lungs, hilar lymph nodes and diaphragm; less frequently the



kidneys and occasionally the heart. The regularity with which tubercles are visible in the diaphragm is a notable feature of the disease whether infection is by the subcutaneous, intraperitoneal or oral route.

As the lesions progress the tubercles enlarge, fuse and eventually, especially in the spleen, liver, lungs and lymph nodes, show central caseation (figures 4 and 5). Ultimately the lesions convert the spleen into a grossly enlarged organ which fills the left side of the abdomen down to the pelvis and shows adhesions to adjacent organs. Macroscopically it shows alternating caseous yellowish masses and hemorrhagic areas. As compared with the normal 0.4 g., it may weigh as much as 11 g. Animals dying after approximately the 200th day frequently also show similar large caseous lesions in the liver and lungs. No involvement of suprarenal glands has been observed.

Oral route of infection: The 2 animals which died on the 317th and 322nd days after being fed with infected tissues showed ulceration of the mucosa of the small gut with tubercles on the corresponding serous surface, involvement of the mesenteric lymph nodes and a spread of tubercles to the other organs including the diaphragm.

C. MICROSCOPIC FINDINGS IN TATERA DYING OF VOLE BACILLUS INFECTION

The earliest lesions consist of small foci of epithelioid cells. These cells have oval, sometimes folded, vesicular nuclei surrounded by an abundant cytoplasm which seldom shows any definite cell border in hematoxylin and eosin preparations. As a result the cells form a continuous mass of cytoplasm and nuclei. They closely resemble the epithelioid cells of tuberculosis but the absence of Langhans type giant cells and the late appearance of caseation are differential features. The lesion in the spleen, lung, lymph node, liver and kidney commonly shows a peripheral zone of round cells which are mainly small lymphocytes but also numerous plasma cells (figure 1). As the follicles enlarge the zone of round cells tends to become less prominent and may disappear entirely (figure 4). In the lung aggregates of lymphoid cells appear to be the first indication of infec-

---

FIG. 1. (Upper left) Early vole bacillus lesion in lung of *Tatera brantsii* showing epithelioid cells and peripheral zone of lymphocytic cells. H. & E. ×138

FIG. 2. (Upper right) Giant cells in the lymphocytic cell zone of vole bacillus lesion in spleen of *Tatera afra*. H. & E. ×198

FIG. 3. (Upper centre left) Spleen in vole bacillus infection of *Tatera brantsii*, showing distribution of the lesions in the Malpighian corpuscles. H. & E. ×39

FIG. 4. (Upper centre right) Peribronchial and perivascular distribution vole bacillus lesions in lung of *Tatera brantsii*. H. & E. ×7

FIG. 5 (Lower centre left) Vole bacillus lesions in kidney of *Tatera brantsii* showing distribution in the cortex of the kidney and in the subepithelial area of the renal pelvis. Caseation in the most advanced lesions is clearly shown. H. & E. ×5

FIG. 6. (Lower centre right) Spread of vole bacillus lesions by regional lymphatic vessels in the inguinal connective tissue of *Tatera brantsii*. H. & E. ×39

FIG. 7. (Lower left) Intracellular organisms in spleen section from *Tatera brantsii* infected with vole bacillus. Ziehl-Neelsen. ×600

FIG. 8. (Lower right) Vole acid-fast bacillus strain D 15. On glycerin gerbil-extract Dorset medium. Four months incubation at 37°C. ×0.6

tion and it is in the centre of these lymphoid aggregates that the epithelioid cell foci appear.

When the lesion is far advanced the tubercles show a tendency to fuse and central caseation becomes apparent. Giant cells are uncommon but they are occasionally observed in the lung and spleen (figure 2) and even less commonly in the liver. They have not been observed centrally or in the epithelioid portion of the follicle but always in the surrounding zone of round cells. The giant cells have a general resemblance to megakaryocytes with large, frequently multilobular nuclei of a vesicular type. The Langhans type of giant cell has not been observed.

The distribution of the lesions in the various organs is remarkably constant. In the spleen the earliest lesions invariably appear in the Malpighian corpuscles (figure 3) and it is only at a very late stage, when the extent and fusion of the lesions destroy the architecture of the organ, that their relationship to the Malpighian corpuscles is lost. In the lung (figure 4) the lesions are peribronchial and perivascular in distribution. In the liver the lesions are most advanced in the portal tracts. But it is also common to find follicles in the hepatic lobules though not in any specific zone. In the kidney (figure 5) the lesions commence in the intertubular connective tissue of the cortex. As they spread they gradually encircle and eventually cause destruction of the tubules but only at a late stage do they invade the glomeruli which often remain isolated in the surrounding lesion. It is common in the kidney to find extensive lesions beneath the pelvic epithelium (figure 5). The earliest lesions in the gut appear in the deeper layers of the lymphoid tissue whence they spread towards the lumen causing ulceration and also through the muscle layer to the serous surface.

The primary site of the lesions in the lymph nodes has not been determined as all the affected nodes which have been sectioned to date have been so extensively involved that the site of the earliest lesions could not be identified.

In the heart the lesions tend to show a perivascular distribution.

The local lesions in the groin appear to extend by lymphatic trunks in the connective tissue and muscles (figure 6). This point requires further investigation but the histological appearances of the disease, wherever it is found, suggest a spread by lymphatic vessels.

A constant and striking feature of the lesions is the weight of the bacterial infection. The organisms, which withstand 25 per cent sulphuric acid and alcohol, are very numerous, even in early lesions. They tend to occur in groups and masses which, in their arrangement, resemble leprosy bacilli. None have been found in the lymphoid aggregates preceding or around the follicles but the epithelioid cells are loaded with organisms many of which are intracellular. When caseation occurs the organisms tend to disappear from the caseous areas but remain numerous in the surrounding epithelioid cells. In spleen smears and sections from infected animals many of the cells are packed with organisms and resemble leprosy cells (figure 7).

D. OTHER SOUTH AFRICAN RODENTS

In addition to *Tatera* two other species of South African rodents were inoculated with vole bacilli in doses ranging from 0.0001 mg. to 0.1 mg. All inoculations were intraperitoneal.

Mystromys albicaudatus: Sixteen *Mystromys* proved totally resistant. All died or were killed between 298 and 749 days after inoculation. In none was any evidence found, macroscopically or microscopically, of infection by vole bacillus.

Mastomys coucha: A group of 17 *Mastomys* was also inoculated intraperitoneally with similar doses. On the thirty-sixth day after inoculation with 0.1 mg. an animal died and showed, on microscopic examination of the spleen, a minute epithelioid cell follicle in a lymph node lying adjacent to the spleen, though the latter organ showed no evidence of infection. Scanty acid-fast bacilli were found in the lesion. A second animal died on the 103rd day after an injection of 0.0001 mg. The spleen smear was positive for acid-fast bacilli. Histological examination of the spleen showed minute epithelioid cell follicles in the Malpighian corpuscles. Suitably stained preparations showed acid-fast bacilli in the follicles. Two animals died on the 298th day after 0.01 mg. but spleen smears and histological examination were negative.

Six animals of this group were killed on the 476th day but were in good condition and showed no sign of disease. On the 623rd day after inoculation with 0.0001 mg. an animal died showing extensive lesions in the lungs, though the animal's general condition was good and no other organs appeared to be affected. An animal showing similar, but less advanced changes, died on the 669th day after 0.1 mg., though 2 which died on the 668th day after a similar amount showed no evidence of infection. The remaining 3 animals, which had received 0.1, 0.01 and 0.0001 mg., respectively, were killed on the 749th day after inoculation. One, which had received 0.01 mg. showed gross lung lesions and a few minute tubercles in the small gut and spleen, but in other respects appeared to be healthy. The other 2 animals were unaffected. Of the 17 animals, therefore, 5 showed lesions, the earliest at thirty-six days and the latest when it was killed at the 749th day. In the 3 most grossly affected animals the lesions were mainly in the lungs. The only lesions found outside the lungs were in the spleen, in the gut and in a focus of lymphoid tissue adjacent to the spleen. In each instance the lesions outside the lungs were microscopic in nature even in the animal which was killed 749 days after inoculation and showed gross lung lesions. The good general condition of the affected animals, with abundant subcutaneous and omental fat, was in striking contrast to the extensive lung lesions in 2 of them.

Histologically the animal which died on the 669th day showed small aggregates of epithelioid cells in the lung similar to those found in *Tatera* except that there was no encircling ring of lymphocytes. The other 2 animals showed lung lesions, however, which were so far advanced that no individual tubercles could be distinguished. Large areas of the lung tissue were replaced by proliferating epithelioid cells and areas of caseation associated with foci of xanthomatous de-

generation. No giant cells were observed. A few foci of lymphoid hyperplasia were present in relation to the epithelioid cell reaction. The vole bacillus was present in great numbers in the lung lesions and scanty acid-fast bacilli were also found in the gut, splenic and lymphoid lesions.

E. GUINEA PIGS AND RABBITS

Guinea pigs: Twenty-one guinea pigs were inoculated intraperitoneally with doses ranging from 0.0001 mg. to 0.01 mg. Eight other guinea pigs were inoculated subcutaneously with 0.25 cc. of a heavy saline suspension of the ground-up viscera of a *Tatera* which had died with extensive lesions. One of the latter group died on the twenty-first day and showed acid-fast bacilli in a spleen smear. This animal, the only one of the series to do so, showed a marked local lesion at the time of its death with caseous areas in the abdominal wall and regional lymph nodes, in both of which sites numerous acid-fast bacilli were found. Some of the other animals showed local lesions with enlargement of the regional lymph nodes two or three weeks after subcutaneous inoculation, but by the time the animal died or was killed the lesion had healed leaving only an área of scar tissue. The other 28 animals of both groups died or were killed at periods ranging from nine to 755 days but none showed any evidence of infection at postmortem examination. Spleen smears were consistently negative with the exception noted above and neither macroscopic nor microscopic lesions were found.

Rabbits: A group of 11 rabbits was negative over a period of 136 to 755 days after intraperitoneal inoculation with 0.0001 mg. to 0.1 mg. vole bacillus culture.

F. SUSCEPTIBILITY OF TATERA TO M. TUBERCULOSIS[3]

In view of the high susceptibility of *Tatera* to vole acid-fast bacillus a series of 75 *T. brantsii* was divided into groups and inoculated subcutaneously with saline suspensions of:

(*a*) Virulent human *M. tuberculosis* (strain E. L. I.).
(*b*) Virulent bovine *M. tuberculosis* (Ferreira-Onderstepoort strain).
(*c*) Avirulent human *M. tuberculosis* (Saranac strain).
(*d*) Avirulent bovine *M. tuberculosis* (BCG strain).

The dosage varied from 0.0001 mg. to 0.1 mg. Unfortunately 26 of the animals died within the first seven days after inoculation and were, therefore, lost from the experiment. It has now been found that early losses are high if gerbils recently trapped and brought into the laboratory are used too soon after capture. Keeping the animals in the laboratory for some weeks before using them reduces losses of this nature. The ideal would be to use laboratory-bred animals in

[3] Since this paper was accepted for publication one of a new group of gerbils injected with 0.1 mg. tubercle bacilli (bovine type) has died, fifty-eight days after inoculation, showing evidence of infection with the organism. It would appear, therefore, that the resistance of the gerbil to tubercle bacilli is not quite so complete as the first group of gerbils seemed to indicate.

which losses are negligible but they do not breed readily enough for this purpose.

At present, 454 days after inoculation, 18 animals survive. One animal died on the twenty-third day and 30 others between the fifty-third and 390th days. Only one showed any evidence of infection with acid-fast bacilli. This was an animal which had been inoculated with 0.01 mg. of the attenuated Saranac strain. It died on the ninety-fifth day and, though negative macroscopically, showed numerous microscopic lesions in the spleen and one or two in the lungs. The hilar root nodes also showed evidence of infection. The lesions were identical with those found in the early stage of vole bacillus infection in these animals, namely, epithelioid cell follicle formation without giant cells or caseation in the Malpighian corpuscles of the spleen and in relation to the bronchi and blood vessels in the lungs. Numerous acid-fast organisms were found in suitably stained preparations of the spleen, lung and root nodes.

G. SUSCEPTIBILITY OF TATERA AND MYSTROMYS TO M. LEPRAE

Sixteen *T. brantsii* and 7 *Mystromys albicaudatus* were inoculated with a saline suspension of the ground-up tissues from lepra nodules in which numerous *M. leprae* were present. The *Mystromys* were observed over periods ranging from ninety-four to 805 days but none showed any evidence of infection macroscopically or microscopically. Of the 16 *T. brantsii*, 6 died between forty-two and 327 days after inoculation showing no sign of infection. The remaining 10 animals, at 327 days, are healthy and are being kept under observation.

II

The Culture of the Vole Acid-fast Bacillus on Medium Containing an Extract of Tatera Tissues

Because of the susceptibility of the gerbil to the vole bacillus, an extract of organs, muscles and blood of this rodent was incorporated in the nutritive media to ascertain whether it would affect the dysgonic character of the organism.

On Dorset medium with or without 1 per cent glycerin, the introduction of the extract resulted in a more rapid and more profuse growth of the strain than on plain or glycerinated Dorset and other media used in our experiments.

Small colonies were observed after a fortnight at 37°C. After two or three months' incubation, two types of colonies developed, resembling in character to some extent those of the bovine types of tubercle bacillus (figure 8).

1: Pyramidal nonpigmented colonies, 4 to 6 mm. in diameter, opaque, with irregular edges, rugose or slightly wrinkled surface, and raised centre.
2: Warty nonpigmented colonies, 3 to 4 mm. in diameter, almost circular, opaque and of somewhat less rugose appearance than the former.

After three or four months' incubation, the colonies showed no further development.

Microscopic examination of films from the two types of colonies showed typical acid-fast vole bacilli. Subcultures on glycerinated gerbil-extract Dorset medium gave colonies with similar characteristics, but not necessarily all of the one type.

Incorporation of gerbil-extract in potato medium gave a warty type of colony, reaching 2 to 3 mm. after two months. Colonies remained isolated on the surface of the potato. In no instance so far have we observed with the vole bacillus any sign of the confluence so characteristic of the human or bovine type of tubercle bacillus on 5 per cent glycerinated potato medium.

Attempts to culture on liquid media, either synthetic, such as Sauton medium, or gerbil-extract broth (with or without glycerin) or a combination of these media have not so far been successful.

Occasionally a fine pellicle of vole bacillus growth developed on the surface of the nutritive gerbil broth at the bottom of the slope or on the walls of the tubes of potato medium. These were transplanted to the surface of synthetic or organic liquid media. They occasionally developed a very fine pellicle but subsequent passages failed to given any appreciable growth.

DISCUSSION

The above findings show that the susceptibility of the South African gerbils to vole acid-fast bacilli is at least as great as that of the English field vole, *Microtus agrestis*. Griffith (1939a), using subcutaneous inoculation of 0.01 mg. to 0.5 mg. of vole bacillus culture and also in animals infected by scarification and others by the oral route, found that, of the 11 voles he used, the animals with positive results showed lesions mainly in the areolar tissue of the groins and axillae. Visceral lesions were tardy in appearance and were not of regular occurrence. The lungs most frequently showed lesions. Only in 2 voles did the spleen show macroscopic lesions. Glandular changes were not conspicuous except in one animal. These findings are in contrast to our results with *Tatera* in which visceral lesions are common and the spleen is the organ most constantly affected, while lesions of the areolar tissue are minimal.

On the other hand, the few *Mastomys* which showed lesions were found, like *Microtus*, to have lesions of the lungs, while the other organs, with the exception of minimal lesions in the gut, spleen and lymphoid tissue of 3 animals, were not involved. *Mastomys*, however, unlike *Microtus* showed no lesions of the subcutaneous areolar tissue.

Another point of contrast is that *Tatera* showed progressive fatal disease after inoculation with as little as 0.0001 mg.

Griffith (1939a) found the English vole more susceptible to infection with bovine *M. tuberculosis* than to that with the vole bacillus. *Tatera*, in our hands, have shown the opposite result in that they are highly susceptible to vole bacillus infection, but none, so far, (with the one exception mentioned) have shown lesions after inoculation with bovine strains of *M. tuberculosis*.

Histologically also there are marked points of contrast between voles and

gerbils infected with vole bacillus. Griffith (1939a), quoting a histologica report by Pagel, emphasizes the absence in voles of epithelioid cell tubercle formation and the presence of extensive necrosis in which numerous acid-fast bacilli are found. Voles infected with human or bovine types of tubercle bacilli, however, showed epithelioid cell tubercle formation. In contrast to these findings the characteristic feature in *Tatera* after inoculation with vole bacillus has been the tubercle formation which, when sufficiently far advanced, leads to caseation, while inoculation with bovine and human bacilli produced no histological change.

Griffith (1939b) also found the golden hamster (*Cricetus auratus*) susceptible to large doses (1 mg.) of vole bacillus subcutaneously but, though tuberculosis-like lesions were produced, there was no caseation. The hamster was even more susceptible to *M. tuberculosis* (both human and bovine) than it was to the vole acid-fast strain and the resulting lesions were characterized by caseation. These results, also, are in contrast to those obtained by us with *Tatera*. Further, *Mystromys*, which is a member of the same sub-family (*Cricetinae*) as the hamster, was wholly resistant to vole bacillus in doses up to 0.1 mg. On the other hand, there is a wide phylogenetic gulf separating the two rodents *Microtus* and *Tatera* which show the greatest susceptibility to vole bacillus. The varied response of different rodent species appears to be a specific one and not a group response of related forms.

The type of infection observed in gerbils infected with the vole bacillus differs markedly from that observed in guinea pigs and rabbits inoculated with bovine strains of the tubercle bacillus. The latter is acute in nature and shows early caseation with definite Langhans type giant cell formation in relation to a marked epithelioid cell reaction. Vole bacillus infection in gerbils, on the other hand, is characterized by a slow progressive lymphatic invasion with epithelioid cell tubercle formation. The few giant cells are not of the Langhans type and caseation occurs only at an advanced stage of the disease. One of the most striking features of the vole bacillus lesions in gerbils is the abundance of acid-fast bacilli similar to that in some cases of leprosy. Griffith (1939b) mentions a similar finding in the golden hamster.

The route of infection appeared to have no bearing on the nature of the disease or the distribution of the lesions in infected gerbils. Subcutaneous, intraperitoneal and oral routes were equally successful in producing infection and in each instance the spread appeared to be by the lymphatics.

The high degree of susceptibility of gerbils to vole acid-fast bacillus is in contrast to their resistance to other acid-fast bacilli including virulent and avirulent human and bovine strains of *M. tuberculosis* and a strain of *M. leprae*. It also contrasts with the complete resistance to vole bacillus infection shown by *Mystromys* and the partial immunity shown by *Mastomys*. Our work corroborated the findings of other workers regarding the relative tolerance of guinea pigs and rabbits to the vole bacillus. (Griffith (1942), Corper and Cohn (1943).) We failed to produce progressive disease in these animals with amounts up to 0.01 mg. It has been recorded by others that even 0.1 to 1 mg. may cause only a retrogressive type of lesion (Griffith (1942), Brooke (1941)).

SUMMARY

1. The susceptibility of the South African rodents *Tatera brantsii*, *Tatera afra*, *Mastomys coucha* and *Mystromys albicaudatus* to the vole acid-fast bacillus has been tested.

2. *Tatera brantsii* and *Tatera afra* have been found highly susceptible. *Mastomys coucha* shows lesions in a minority of inoculated animals. *Mystromys albicaudatus* has proved unsusceptible.

3. The microscopic and macroscopic appearances in *Tatera* infected subcutaneously, intraperitoneally and orally are described.

4. The susceptibility of *Tatera brantsii* to virulent human and bovine strains and to the Saranac and BCG avirulent strains of *M. tuberculosis* was also studied.

5. The only positive result in this group of *Tatera* was an animal inoculated with the Saranac strain.

6. The susceptibility of rabbits and guinea pigs to the vole acid-fast bacillus was tested and, as previously reported by other workers, found to be of a low order.

7. A group of 16 *Tatera* and 7 *Mystromys* was inoculated with a suspension of *M. leprae* from a lepra nodule. No evidence of infection has been observed in any animal up to 327 days.

8. The addition of an extract of *Tatera* tissues to Dorset's medium markedly improved the growth of the vole acid-fast bacillus.

SUMARIO

1. Comprobada la susceptibilidad de los roedores sud-africanos *Tatera brantsii*, *Tatera afra*, *Mastomys coucha* y *Mystromys albicaudatus* al bacilo ácidorresistente del *Microtus arvicola*, los *T. brantsii* y *T. afra* resultaron muy susceptibles, en tanto que el *Mastomys coucha* mostró lesiones en la minoría de los animales inoculados y el *Mystromys albicaudatus* resultó insusceptible.

2. Descríbese el aspecto micro y macroscópico de las tateras infectadas subcutánea, intraperitoneal y oralmente.

3. También se estudió la susceptibilidad de la *Tatera brantsii* a cepas humanas y bovinas virulentas y a las cepas Saranac y BCG avirulentas del *M. tuberculosis*.

4. En este grupo de tateras el único resultado positivo fué en un animal inoculado con la cepa Saranac.

5. Comprobada la susceptibilidad de los conejos y los cobayos al bacilo ácidorresistente del *M. arvicola*, resultó escasa según han comunicado previamente otros investigadores.

6. A un grupo de 16 *Tateras* y 7 *Mystromys* se les inoculó una suspensión de *M. leprae* de un nódulo leproso, sin observarse signos de infección en ningún animal ni aun a los 327 días.

7. La adición de un extrato de tejidos de *Tatera* al medio de Dorset acrecentó decididamente la proliferación del bacilo ácidorresistente del *M. arvicola*.

Acknowledgments

Our grateful thanks are due to Dr. F. W. Simson for much helpful advice and criticism in the course of this work; to Dr. A. R. Davison of the Pretoria Leper Institution for the leprosy material used; and to Mr. F. A. Brandt for the microphotographs.

REFERENCES

BROOKE, W. S. (1941): Am. Rev. Tuberc., 1941, *43*, 806.
BROOKE AND DAY (1944): Bull Johns Hopkins Hosp., 1944, *74*, 275.
CORPER, H. J., AND COHN, M. L. (1943): Am. J. Clin. Path., 1943, *13*, 18.
GRIFFITH, A. S. (1939a): J. Hyg., 1939, *39*, 244.
GRIFFITH, A. S. (1939b): J. Hyg., 1939, *39*, 154.
GRIFFITH, A. S. (1942): J. Hyg., 1942, *42*, 527.
WELLS, A. Q. (1937): Lancet, 1937, *1*, 1221.

PULMONARY ACARIASIS

Its Relationship to the Eosinophil Lung and Löffler's Syndrome

A. VAN DER SAR[1]

The syndrome "Tropical Eosinophilia" (Weingarten (1)) has been reported from different parts of the world, for example, East Indies, India, Cuba and the Netherland West Indies. However, up to the present, three different causes have been found for the same syndrome, for instance, de Langen (2) (1927) in the Netherland East Indies found a severe infection with *Strongyloides stercoralis*. In the sputum of one of his patients a strongyloid larva could be observed. The patients were treated with tartar emetic injections and all symptoms promptly subsided.

Meyers and Kouwenaar (3) (Netherland East Indies) demonstrated in 1939 *Microfilaria Malayi* in the enlarged lymph nodes of the groin. Only in a few was the spleen enlarged.

In the Netherland West Indies, van der Sar and Hartz (4), in 1945, also proved the relationship between tropical eosinophilia and microfilaria. In 2 cases (one unpublished) they found microfilaria in the enlarged axillary lymph nodes. The first patient was treated with tartar emetic; a recurrence followed after two months; treatment with Mafarside caused the symptoms to disappear completely. In the second patient, also treated with Mafarside, the symptoms disappeared and, after six months, no recurrence developed.

At Ceylon, in 1944, Carter, Wedd and D'Abrera (5) examined the sputa of 28 patients suffering from respiratory complaints. The eosinophil count in the peripheral blood varied from 6 to 66 per cent. They demonstrated various types of mites in the sputa of 17 out of 28 patients.

Soysa and Jayawardena (6) (1945) observed 30 Ceylonese soldiers suffering from asthmatic bronchitis with attacks of severe dyspnea, particularly at night. The hematological examination revealed a leucocytosis which ranged from 10,200 to 37,000, while the eosinophil count varied between 33 and 81 per cent. An enlarged spleen or enlarged peripheral lymph nodes were not noticed. Mites of either *Tyroglyphus* or *Tarsonemus* were recovered from 11 sputa out of 21 cases examined.

On the basis of the observations made by Carter *et al.*, Soysa and Jayawardena, the possibility of a mite infection in our cases with asthmatic conditions, but without an enlarged spleen or enlarged lymph nodes, could be expected. An investigation of several patients revealed the following results.

CASE REPORTS

Eight cases were examined, their age ranging between 8 and 48 years.

Cases 1, 2, 3, and 4 had one principal symptom in common, namely asthmatic bronchitis. The asthmatic bronchitis grew worse at night and a tenacious, mucopurulent sputum

[1] Internist of the Public Health Service, Curaçao, N. W. I.

was raised. Symptomatic treatment was without benefit. An enlarged spleen or enlarged lymph nodes were not noticed.

Case 5 was admitted to the hospital while he raised some blood with the sputum. He had no history of tuberculosis. During the last twelve months he complained of recurrent bronchitis without asthma. Examination of the throat and larynx revealed nothing abnormal. The spleen and lymph nodes were not enlarged.

Cases 6 and 7: The histories of these two sisters revealed repeated attacks of bronchitis which did not disappear after the usual symptomatic treatment. Family history of tuberculosis was negative. The spleen was not enlarged, but small lymph nodes were palpable in the left and right axilla.

In these cases the environment was of special interest, for in the same building, two and three years before, 2 patients were observed with typical tropical eosinophilia, without enlarged spleen and enlarged lymph nodes. The leucocyte counts ranged between 15,000 and 40,000 with an eosinophilia of 62 and 70 per cent, respectively. At that time no cause could be found. They were successfully treated with injections of tartar emetic.

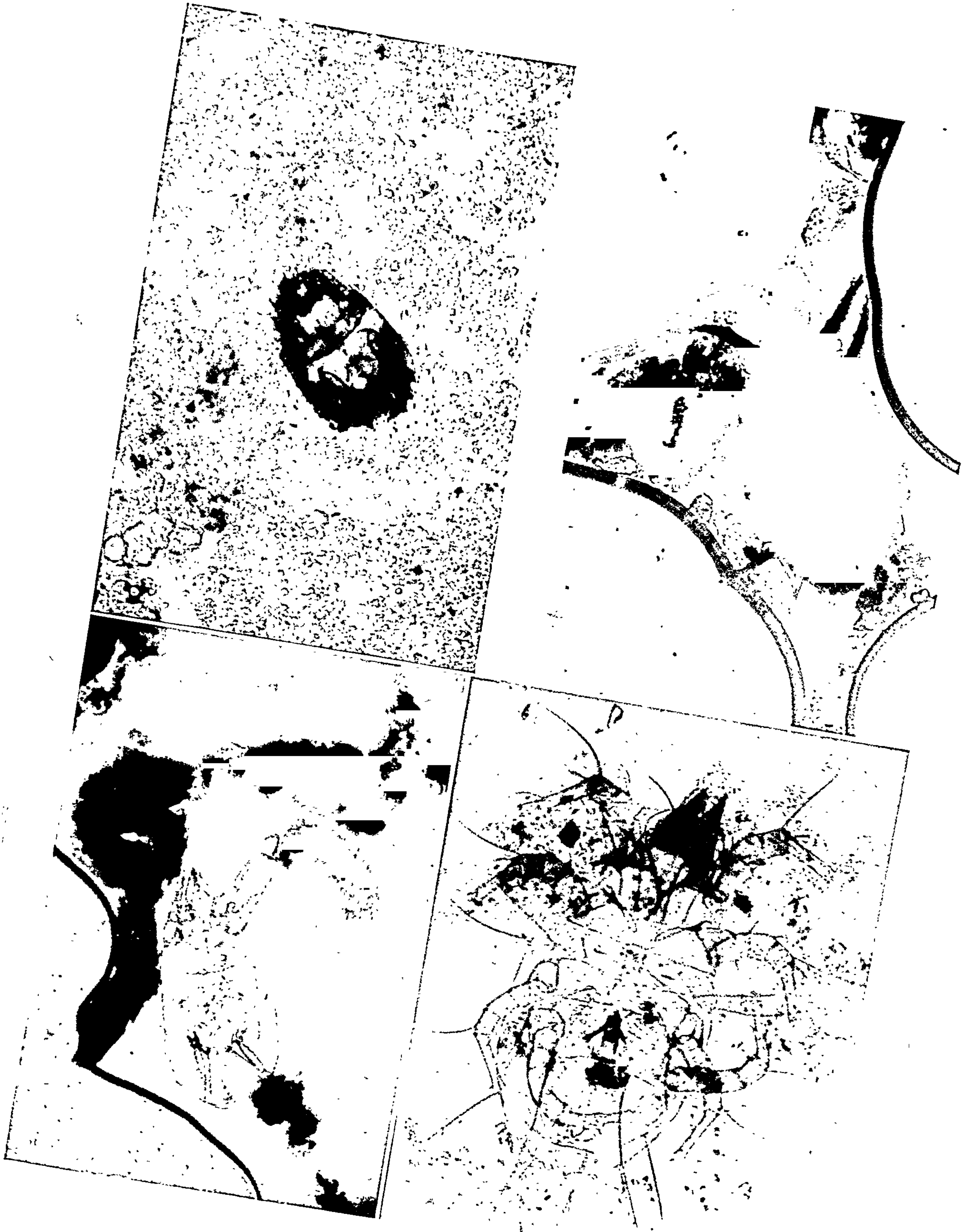
Case 8: Two years ago he contracted a tuberculous infection of the right lung. There was a small cavity in the right upper lobe and a dense infiltration in the lower one. Sputum examination revealed acid-fast bacilli and the animal test for tuberculosis with this sputum was positive.

A pneumothorax was induced and a satisfactory collapse of the lung was obtained. On admission, the blood count was normal without eosinophilia. Four months after the pneumothorax was started, the sedimentation rate rose and the white blood count was 13,600 with 26 per cent eosinophil cells. This blood count varied considerably, for example, on March 3, 1945, 18,500 leucocytes with 4 per cent eosinophils and on July 16, 1945, 17,400 leucocytes with 14 per cent eosinophils. The elevated sedimentation rate (36 mm.) was not explained by the X-ray appearance of the lung. Sputum was negative for acid-fast bacilli, as was also the animal test. The spleen was never enlarged but some lymph nodes of pea-size were present in the right axilla. During the latest elevation of the leucocyte count, mites, different from the type found in the other cases, could be recovered from the sputum.

LABORATORY EXAMINATIONS

The stools were repeatedly examined for parasites and ova without positive results. Examination of the sputum of all patients, with the Ziehl-Neelsen method, was negative. In the gastric contents of cases 5, 6, 7 and 8 acid-fast bacilli could not be found with the Ziehl-Neelsen method, on culture and animal inoculation. Nightly blood examinations for filariasis were negative.

Sputum examination for mites: Before the sputum was collected, all precautions against contamination by mites from extraneous sources were taken, as mentioned by Soysa. Preparation of the sputum was carried out according to the method described by Carter *et al.* All the sputa were found to be positive for mites. The mites of cases 2, 3, 4, 5, 6 and 7 are, according to Belding *et al.* (7), possibly hypopal stages (see figures 1, 2 and 3). The mites found in case 8 are of a different type and are still not identified. Only in case 1 was the adult form of *Tyroglyphus* (probably the female) found (figure 4).



X-RAY FINDINGS

The roentgenological findings consisted in 5 cases (1 to 5) in the so-called eosinophil lung; in 2 cases (6 and 7) in transient pulmonary infiltrations, both localized in the left lung; in case 8 no pulmonary infiltration or catarrhal reactions could be observed.

The eosinophil lung (figures 5 and 6) was characterized by enlarged hilar-markings, fine mottling with ill defined spots, mostly disseminated through both lungs; this however is not necessary. A catarrhal reaction of the finer lung markings was nearly always present. In cases 6 and 7 transient pulmonary infiltrations could be observed (figures 7 and 8); in case 6 these infiltrations were found in the base of the left lung, in case 7 there was a large hilar infiltration of the left lung.

After treatment, the lungs in all cases were clear.

HEMATOLOGICAL OBSERVATIONS

The hematological examinations showed great variation (see table 1). The total leucocyte count ranged between 12,000 and 20,700, the lowest percentage of eosinophils was 1 per cent, the highest 80 per cent. A mild degree of secondary anemia was sometimes present. Eosinophilic leukemia could easily be discarded because all the eosinophil cells were of the mature type.

TREATMENT

Patients 1 to 5 were treated with Mafarside injections every five days. The symptoms promptly disappeared but the eosinophil count was, at the end of the treatment, still higher than normal. The hemoglobin content returned to normal levels; the lack of appetite disappeared; all patients gained weight.

Patients 5, 6, 7 and 8 were treated with carbason, three times a day for ten days. They also showed a good response to therapy. No recurrences were observed.

COMMENT

Transient pulmonary infiltrations with a paucity of symptoms and clinical signs, associated with varying degrees of peripheral eosinophilia, form the syndrome as originally described by Löffler in 1932.

Several authors observed the same syndrome, however, associated with an infection with *Entamoeba histolytica* (Hoff and Hicks (8)), with *Strongyloides intestinalis* (Beck (9)), with some allergen (Karan (10)), with cutaneous helminthiasis (*Ankylostoma braziliense*) (Wright and Gold (11)).

Löffler, in reviewing his 51 cases, found 5 different types of pulmonary infiltrations, namely, uni- or bilateral infiltrations, small infraclavicular infiltra-

---

FIGS. 1, 2 and 3. (Upper left; upper right; lower left) Hypopal stages, observed in cases 2 to 7. × 190

FIG. 4. (Lower right) Adult form (probably female) of family Tyroglyphidae, genus probably Tyroglyphus, as observed in case 1. × 399

tions, uni- or bilateral densities or sharply defined densities in the right middle lobe and infiltrations identical with the adult type of tuberculosis.

About the anatomy of these infiltrations nothing was known. Martens and Engelbreth-Holm (12) were of the opinion that these infiltrations were anaphylactic edema or infarcts.

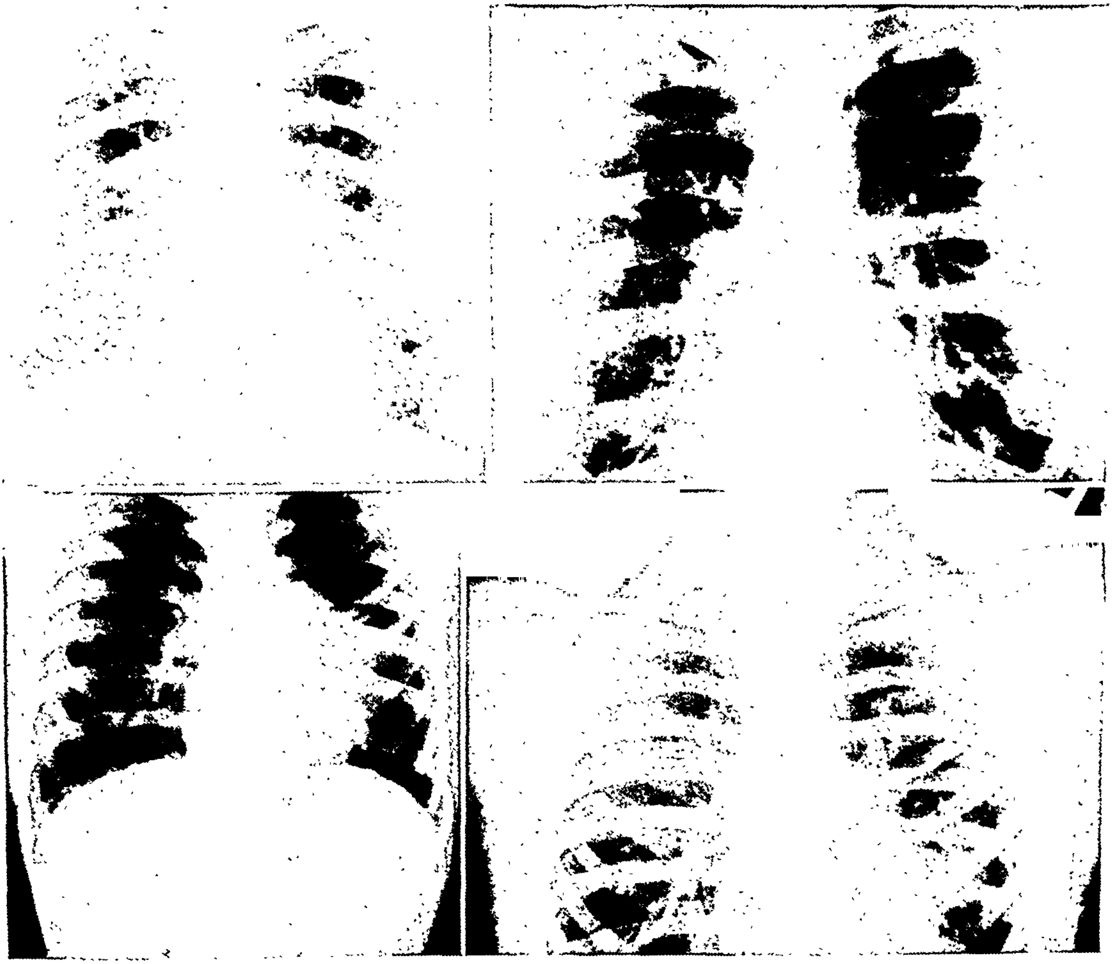


FIG. 5. (Upper left) Case 2. Typical eosinophil lung with enlarged hilar markings; small ill defined spots are visible on both sides.

FIG. 6. (Upper right) Case 5. Eosinophil lung, mostly right-sided and in the base.

FIG. 7. (Lower left) Case 7. Transient left-sided hilar infiltration (Löffler's infiltration).

FIG. 8. (Lower right) Case 7. The X-ray film of the lungs one week after treatment with carbason.

Meyenburg (13), in 1942 published his pathological findings in 5 cases. Four of them were soldiers killed by accident; they were previously in good health. The fifth case died of a tetanus infection. On gross examination he found bronchopneumonia without any special characteristics. On microscopical examination, however, it was found that the lesions consisted of exudative eosino-

philic inflammations. Giant cells with multiple nuclei were a regular finding. They developed from fused alveolar cells, encircling a small vacuole in which no foreign body was ever found. An eosinophilic bronchitis and bronchiolitis was present in 2 cases, the veins in the interlobular septa were also inflamed; there were small thrombophlebitides, but the vessels were never totally closed. He concluded that Löffler's infiltrations may be real eosinophilic bronchopneumonias originating from bronchogenic infection.

These findings of Meyenburg and the occurrence of mites, in hypopal stages and in the adult form, in sputum associated with transient lung infiltrations

TABLE 1

Results of blood counts

CASE NUMBER	SEX	AGE	DURATION OF ASTHMA	OCCUPATION	HEMOGLOBIN CONTENT	RED CELLS	WHITE CELLS		EOSINOPHILIA		SEDIMENTATION RATE FIRST HOUR
							Initial	Final	Initial per cent	Final per cent	
		years			*per cent*						*mm.*
1. P. N....	Female	48	4 months	Housewife	85	4,400,000	20,200	4,500	61	8	25
2. B. H....	Male	37	3 months	Clerk	96	4,940,000	19,900	7,900	58	7	10
5. V. K....	Male	41	3 weeks	Policeman	91	4,840,000	20,700	7,800	58	8	18
4. C. J....	Male	41	5 weeks	Laundry-worker	103	5,310,000	18,000	6,800	80	4	56
5. G. J....	Male	34	No asthma	Electrician	82	4,190,000	13,400	9,100	18	5	16
6. W. E....	Female	8	Bronchitis		70		14,600	7,700	1	8	32
7. W. R...	Female	9	Bronchitis		79	4,100,000	12,000	7,700	17	11	30
8. F. B....	Male	42	Bronchitis	Laborer	91	4,580,000	17,400	8,200	14	4	36

stress the possibility that mite infection is of pathognomonic significance. We are supported in this opinion by the demonstration of pulmonary lesions in monkeys (Davis (14)). He suggested that the ill defined spots, as seen on X-ray films, may result from lesions similar to those described in monkeys. Nothing however is known about the hematology in monkeys with pulmonary acariasis.

The question why in some cases the mite infection manifests itself as tropical eosinophilia, in other cases as Löffler's syndrome and, as in our case 8, without any roentgenological abnormalities while a leucocytosis with eosinophilia persisted, must remain unanswered for the time being.

SUMMARY

The demonstration of mites in the sputum of 8 patients confirmed the findings of Carter *et al.*, and Soysa and Jayawardena.

Löffler's syndrome, hitherto not observed in mite infections, could be demonstrated in 2 cases; they were of the unilateral left type.

The possible pathological significance of mite infection in human beings is supported by the findings of Meyenburg, by the pulmonary lesions caused by mites in monkeys and the raising of blood with the sputum in one of our patients.

SUMARIO

La demostración de ácaros en el esputo de ocho pacientes confirmó los hallazgos de Carter et all y Soysa and Jayawardena.

El síndrome de Löffler, hasta ahora no observado en las infecciones por los ácaros, pudo ser demostrado en dos casos, eran del tipo unilateral izquierdo.

La posible importancia patólogica de la infección por ácaros en seres humanos es apoyada por los hallazgos de Meyenburg, por las lesiones pulmonares causadas por los ácaros en monos y la excreción de sangre con el esputa en un de nuestros pacientes.

We are indebted to Prof. Dr. David L. Belding, Dr. J. C. Bequaert and Mr. Nathan Banks of the Boston University for the determination of the mites.

REFERENCES

(1) WEINGARTEN, R. J.: Tropical eosinophilia, Lancet, January 23, 1943, *244*, 103.
(2) DE LANGEN, C. D.: Anguillosis en het ziektebeeld van de "Idiopathische Hypereosinophilie", Geneesk. tijdschr. v. Nederl.-Indië, 1928, *67*, 973.
(3) MEYERS, F. M., AND KOUWENAAR, W.: Over hypereosinophilie en over een merkwaardige vorm van filariasis, Geneesk. tijdschr. v. Nederl.-Indië, 1939, *79*, 853.
(4) VAN DER SAR, A., AND HARTZ, PH.H.: The syndrome Tropical Eosinophilia and microfilaria, Am. J. Trop. Med., March, 1945, *25*, No. 2.
(5) CARTER, H. F., WEDD, G., AND D'ABRERA, V. ST. E.: The occurrence of mites (acarina) in human sputum and their possible significance, Indian. M. Gaz., 1944, *79*, 163. (Abstract in Trop. Dis. Bull., 1945, *42*, 73.)
(6) SOYSA, E., AND JAYAWARDENA, M. D. S.: Pulmonary acariasis: A possible cause of asthma, Brit. M. J., January 6, 1945, p. 1.
(7) BELDING, D. L. *et al.*: Personal communication.
(8) HOFF, A., AND HICKS, H. M.: Transient pulmonary infiltrations: A case with eosinophilia (Loeffler's syndrome) associated with amoebiasis, Am. Rev. Tuberc., 1942, *45*, 194.
(9) BECK, CLAGETT L.: The Loeffler syndrome: Report of a case, Hawaii M. J., July, 1942, p. 361.
(10) KARAN, A. A., AND SINGER, E.: Transitory pulmonary infiltrations mistaken for tuberculosis: With report of five cases, Ann. Int. Med., 1942, *17*, 106.
(11) WRIGHT, D. O., AND GOLD, E. M.: Loeffler's syndrome associated with creeping eruption (cutaneous helminthiasis), J. A. M. A., 1945, *128*, 1082.
(12) MARTENS AND ENGELBRETH-HOLM: l.c. Meyenburg.
(13) MEYENBURG, H.: Das eosinophile Lungeninfiltrat, Pathologische Anatomie und Pathogenese, Schweiz. med. Wchnschr., 1942, *72*, 809.
(14) DAVIS, L. J.: Pulmonary acariasis in monkeys, Brit. M. J., April 7, 1945, p. 482.

AMBULATORY PNEUMOTHORAX INDUCTION

A Report of One Year's Experience in Chungking

ADELE COHN WRIGHT[1]

For the city of Chungking with a population of over 1,000,000 there are less than 200 beds available for tuberculosis patients. With so few beds, none of which is free, it is obvious that the number of patients who can obtain hospital care is insignificant. Because of the prevailing social and economic conditions, to be described below, bed-rest at home is practically impossible. It seemed, therefore, that the only hope under these circumstances was ambulatory pneumothorax treatment. Since there were no hospital facilities to take care of patients during the period of pneumothorax induction, it was decided to perform the inductions, as well as the refills afterwards, in the clinic. In this way, a number of patients could be treated who were suitable for pneumothorax therapy but unable to obtain it because of the lack of hospital facilities, the expense of hospitalization and their inability to afford interruption from work for the period of treatment. It was hoped that this method of treatment might lead to cure or at least prolongation of life for the individual patient while at the same time it would serve an important epidemiological function by converting open cases into closed cases.

LIVING CONDITIONS IN CHUNGKING

Chungking, previously a small up-river city of about 300,000 inhabitants, became China's wartime capital in 1938. Since then its population has grown steadily and now numbers over 1,000,000. Many of these are refugees who have flowed into Chungking in successive waves following the loss of territories in other parts of the country to the Japanese. Living quarters, often dark and poorly ventilated, are extremely congested, with sometimes one or two families sharing one small room. Some parts of the population live in dormitories provided by their employers and take their meals at a community table. Very few buildings have running water, and even so the supply is usually turned off for the greater part of the day. For the majority of the population, drinking and washing water has to be fetched in buckets from the river or from pumps at scattered points in the city. The form of toilet generally used is an earthenware jar, the contents of which are emptied daily into buckets, carried through the streets to the river where they are emptied into boats for transportation outside the city to be used for soil fertilization. There is no adequate garbage disposal and rats and flies flourish unchecked. Summers are hot and humid. In winter, which is damp and cold, rooms are entirely unheated except for those who can afford a charcoal brazier. Transportation facilities consist in rickshaws and a limited number of overcrowded buses. Travelling—the city, being built on two

[1] Since September, 1941, Tuberculosis Consultant to the Chinese Red Cross, under the auspices of the American Bureau for Medical Aid to China.

sides of a ridge, is full of steep gradients—is quite strenuous and becomes an mportant consideration in ambulatory treatment. The most serious problem, however, is nutrition. One might almost say that malnutrition is the rule, except for the well-fed few, and is obviously the leading cause for the high incidence of tuberculosis in Chungking and other cities in China. Beans and rice are the main diet of a large part of the population. Because of inflationary costs, many people scarcely ever eat meat, eggs, fats or fish. Finally, lack of education, large numbers of the population being unable to read or write, and particularly lack of health education, with indiscriminate spitting, present serious problems.

THE CLINIC

The Tuberculosis Clinic of the Chinese Red Cross Society, located in the heart of the city, is the only clinic of its kind in Chungking. A similar clinic, operated by the National Institute of Health, is situated 17 kilometers outside Chungking and is inaccessible because of the lack of transportation facilities.

The clinic opened on June 13, 1944. With the assistance of a full-time graduate nurse, the writer took histories, prescribed treatment and performed all pneumothorax treatments. All fluoroscopic examinations were done by the writer and sputum examinations were made by a laboratory technician. The clinic was open five days a week from 8 a.m. to 12:30 p.m. and 2 p.m. to 4 p.m. In January, 1945, a physician, who had been trained by the writer for a three-month period in 1943 to do pneumothorax work, came to help and has since done all refills and alternate initials.

Since there were no X-ray films available, diagnosis had by necessity to be made on fluoroscopic findings. For fluoroscopy, a small slow screen, 8″ x 10″, held in the hands, and a portable X-ray machine are used. The writer fluoroscoped all patients until last fall, since which time a good technician, with an amazing acuity for detecting small lesions but with no medical training necessary for diagnosis, fluoroscopes all new patients and refers for reëxamination by the writer only positive or suspected cases. The fluoroscope runs on city current which is shut off four to five days a week in the section of Chungking in which the clinic is located. Rarely a patient is fluoroscoped the first time he comes to the clinic, more often he must obtain a reservation for fluoroscopy a week to ten days later. Interruption of the current is not according to any schedule and quite unpredictable, so that after repeated visits on noncurrent days many patients get discouraged and never return for fluoroscopy.

Following fluoroscopic examination, patients are told the nature of their disease and provided with instruction sheets regarding simple measures of hygiene. Patients who cannot read are given basic verbal instructions by the nurse. In general, it is most important that the patient be immediately given definite information concerning his disease. Because of a lack of education the patient does not understand that his condition may be active or inactive or possibly nontuberculous, so that, unless he obtains positive information, there is a good chance that he will be lost track of and ignore his disease or go to a private doctor who will generally prescribe intravenous calcium preparations at exorbitant prices and expensive nonspecific drugs. Patients with frankly active

and cavitary disease are no problem and, if there is the slightest possibility that pneumothorax can be done, that treatment is suggested. To help the patient understand the purpose of pneumothorax treatment, he is shown a large chart with schematic representations of cavitation, before, during and after pneumothorax treatment. Minimal lesions are always considered active until proved otherwise and, if the patient does not live too far, a minimum of three sputum examinations is required. Smears only are done, the clinic laboratory being unable to do concentrates. Gastric lavages are not done since there are no facilities. Repeated fluoroscopic examinations at four- to six-week intervals are the usual method by which activity can be determined, but in many instances patients put off coming back for check-up for several months.

The work done in the clinic for the year is listed as follows:

Number of clinic sessions	241	
Patients seen for the first time	4,796	
Patients returning for check-up etc.	2,962	
Pneumothorax treated patients	2,597	
Total patients	10,355	
Total fluoroscopies (exclusive of technician's)	7,318	
Total pneumothorax inductions	269	
Total number sputum examinations	818	
Total number first-visit patients fluoroscoped	4,081	
Total number of patients positive for tuberculosis	1,645	(40.3 per cent)
Extent of disease in positive patients (1,645)		
Minimal	723	(43.9 per cent)
Moderately advanced	548	(33.3 per cent)
Far advanced	374	(22.7 per cent)
	1,645	
Total number male patients fluoroscoped	3,394	
Total number male patients positive	1,384	(40.7 per cent)
Minimal	623	(46.6 per cent)
Moderately advanced	461	(33.3 per cent)
Far advanced	300	(20.1 per cent)
Total number of female patients fluoroscoped	687	
Total number of female patients positive	261	(37.9 per cent)
Minimal	100	(38.6 per cent)
Moderately advanced	87	(33.3 per cent)
Far advanced	74	(28.1 per cent)

AMBULATORY PNEUMOTHORAX INDUCTION

Forty-two patients received pneumothorax in the clinic after induction in a hospital. During the clinic year, pneumothorax was induced in clinic in 259

patients, 10 of whom had bilateral pneumothorax induction. There were 45 females (17.8 per cent), 2 of whom were pregnant at the time of pneumothorax induction, and 214 males (82.2 per cent). The oldest patient was 43, the youngest 10 years of age. The age incidence of the entire group was as follows:

10 to 19	18 (6.9 per cent)
20 to 29	159 (61.4 per cent)
30 to 39	81 (31.3 per cent)
40 or more	1 (0.4 per cent)

The occupations of these patients were as follows:

Clerical workers	79
Housewives	25
Shopkeepers	24
Artisans	21
Students	19
Manual laborers	17
Soldiers	17
Domestics	16
Policemen	12
Teachers	8
Miscellaneous	19
Unemployed	2

In 126 patients (49.0 per cent) the original disease at the time of pneumothorax induction was bilateral. In these patients the worse side was always treated first and, failing to find a space, contralateral pneumothorax was attempted with the hope of eventual thoracoplasty on the worse side. There were 10 bilateral pneumothoraces attempted, 5 of which followed failure on the worse side, and 5 of which were simultaneously continued.

The indications for pneumothorax induction were:

Cavitation	193 (74.5 per cent)
Suspected cavitation	14 (5.5 per cent)
Positive sputum	30 (11.5 per cent)
Hemorrhage	13 (5.1 per cent)
Progression	8 (3.1 per cent)
Spontaneous pneumothorax	1 (0.3 per cent)

METHOD OF AMBULATORY INDUCTION

Patients for ambulatory initial induction are required to appear for treatment on three successive days. Interruption of work is not necessary but when possible a week's leave of absence is suggested. There is no preliminary sedation unless cough is intractable and, then, dionin 0.01 g. is given. A Davidson pneumothorax apparatus is used. The patient is told not to move, cough or speak. With the patient lying on his side, a small pillow placed under the unaffected side, the anterolateral chest wall is painted with iodine. The operator wears no gloves. Generally the fifth intercostal space in the anterior axillary line is the site selected. After superficial anesthesia with 2 per cent novocain,

an 18-gauge needle with a long, sharp bevel is used to penetrate the skin and superficial tissues. Then a 2-inch length 18-gauge needle with a short bevel is attached to a 2 cc. syringe filled with novocain and slowly inserted into the chest wall. (The fact that the needle is not entirely blunt permits easy penetration of the subcutaneous tissues and fascia, no force being required, and there is not the sudden, uncontrolled penetration that usually occurs with a blunt needle without a bevel.) The penetration is slow and with a little experience it is generally possible to tell when the parietal pleura has been reached by the feeling of a slight give and pressure on the plunger of the syringe will permit a free flow of novocain into the pleural space. A reading is taken, after removing the syringe and immediately covering the open needle with the index finger. Free readings, negative on both inspiration and expiration, are required and then air is given. The first time 300 cc. of air are given with readings taken at 100 cc. intervals. In cases with hemorrhage, 500 to 800 cc. are given at the first induction. If, however, at any time during the penetration of the chest, blood is aspirated into the syringe or the patient coughs, the needle is withdrawn and another attempt made the next day. After all initial attempts, the patient rests on the table for ten minutes with the pillow placed under the head. For control of cough and pain, the patient is given a three days' supply of dionin. The second and third inductions are performed on subsequent days, giving 600 and 800 cc., respectively, unless dyspnea or poor readings with smaller amounts of air contraindicate these procedures. At first, in patients in whom no free pleural space was found on the first two attempted inductions (in the midaxillary line in the fifth intercostal space for the second attempt), a third attempt was made in the posterior axillary line in the same interspace, but the few cases in which a space was obtained and the ineffectiveness of the space (either pocket or contraselective pneumothorax) led to the abandoning of the third attempt. After the third successful administration of air or the second failure, the patient is fluoroscoped, or, if there is no current, fluoroscoped as soon as possible afterward.

AMBULATORY REFILLS

Since there is no hospital to which patients receiving pneumothorax may go when accidents, such as traumatic pneumothorax, occur, special care is taken in giving refills and, although the method is slower, the initial technique is continued, omitting the rest period. While, in principle, ambulatory refills are conducted the same as those done on bed-rest patients, larger refills are required, usually 800 to 1,000 cc. at weekly intervals for the first month. Since the patients are pursuing their normal activities a large amount of air is used up and besides it is asking the impossible to expect patients to come twice a week under the transportation difficulties of Chungking. At all times negative readings are maintained. Pneumothoraces with contraselective collapse are quickly abandoned after a trial period, with fluoroscopy both before and after refills. Fluoroscopies can only be done for every third refill because of the current shortage. Supplementary food, consisting of bean milk powder, maltose and eggs, is given all pneumothorax patients. This is made possible by a bimonthly grant from

the British United Aid to China Fund. For a short period vitamin A and D capsules provided through the same Fund were supplied to these patients. The Fund also makes possible the large quantities of dionin and codeine necessary for all patients.

RESULTS OF AMBULATORY INDUCTIONS

In general, the initial period is tolerated well. Pain is the most common complaint, usually occurring a few hours after induction. Only one patient (58374) had severe pain immediately after induction. She was observed in clinic for one hour afterward and given dionin. There was no dyspnea. The author's experience with Chinese patients does not lead her to share the common belief that the Chinese are a peculiarly stoical and phlegmatic race, so that, in her opinion, the mildness of the reactions after initial induction cannot be attributed to an exceptionally high threshold to pain among the Chinese.

There were no known induction fatalities. Only one patient (31383) had syncope when getting off the table. Further questioning revealed that the patient had been unable to eat for several weeks because of epigastric discomfort. No cases displayed neurological phenomena.

In 5 patients there developed known traumatic pneumothoraces. Two patients (29665 and 39755) had been given no air because of unsatisfactory initial readings. When seen the following day, pain and dyspnea were complained of and fluoroscopy showed a small marginal collapse in both instances. Three patients (53661, 58265 and 62469) obviously had dyspnea when seen the next day and all showed about 50 per cent collapse on fluoroscopy and required deflation. The subsequent course in each of these patients has been uneventful. Subcutaneous emphysema occurred so infrequently and to such a slight degree as to be insignificant.

Pneumothorax space was obtained in 202 (69.2 per cent) inductions. In 17 patients the results are unknown because of failure to return either to continue treatment or for fluoroscopy after the third initial. Failure to return is in some instances due to misunderstanding, in others because of pain. All patients are warned of the possibility of dyspnea occurring after they return home and are instructed to return for deflation if dyspnea should occur. Results cannot, of course, be evaluated. But it may be mentioned that, on the basis of fluoroscopic findings within two weeks after induction, 94 patients had what appeared to be a therapeutically promising pneumothorax.

CONCLUSIONS

Ambulatory pneumothorax inductions and refills are by no means an ideal treatment, but there is obviously a great need for the method under the present conditions in China, now and for the reconstruction years to follow until adequate hospital facilities can be provided. There is no reason why the *technical* results of pneumothorax induced in clinic should differ from those done under a sanatorium regimen. Of course, the final results in this series cannot be judged, since the duration of the period of observation is too short, but among patients

in this series there have been several cavity closures and many patients have shown symptomatic improvement, all of which is most encouraging. Pneumonolyses could not be performed because of lack of equipment.

There have been patients in the series who have done badly, with progression, contralateral spread and profound toxemia, but that is not the fault of the method alone; some patients do badly under the best of conditions.

Transitory fluids do not seem to occur with greater frequency than in patients in sanatoria. Thus far only 5 patients of the series have shown fluid accompanied by constitutional symptoms, especially fever. Three of these patients had sterile, serous fluid on diagnostic aspiration. Two had empyema; one of these cleared up on clinic treatment alone with complete reëxpansion of the lung in three months. The second empyema patient was sent to a general hospital because he had no facilities for bed-care at his dormitory. He died suddenly three weeks after the onset of the empyema. The smears of the first empyema patient were repeatedly negative for tubercle bacilli and pyogenic organisms, while the pus in the second patient showed *Staphylococcus aureus*.

SUMMARY

1. Because of lack of hospital facilities and poor general conditions in Chungking, ambulatory pneumothorax, including inductions, was attempted during the year beginning June 13, 1944.
2. There were 269 ambulatory inductions in 259 patients.
3. The patients selected and the method of induction are described.
4. There were no accidents in the series.
5. The results are encouraging and warrant further trial in cities where conditions similar to those in Chungking exist.

SUMARIO

1. Debido a la falta de hospitales y malas condiciones generales en Chungking, se inició el neumotórax en forma ambulante durante el año que comenzó en junio 13, 1944.
2. A 259 enfermos se les hicieron 269 tratamientos ambulantes.
3. Descríbense la selección de los enfermos y la técnica utilizada.
4. No hubo accidentes en la serie.
5. El resultado es alentador y justifica otros ensayos en poblaciones en condiciones semejantes a las que existen en Chungking.

PHOTOROENTGENOGRAPHIC RESULTS[1]

A Comparison of the 4 x 5″ and the 70 mm. Equipment in 1,713 Cases

FREDERICK TICE

While fully aware of the value of the routine case-finding methods, it has always seemed to us that X-ray examination of large, extraclinical groups in economically substandard areas represented the ultimate objective. The mortality figures pointed the way and a study of our tuberculosis spot maps for the Chicago area confirmed still further our conviction that mass X-raying of the decadent neighborhoods, supplemented with the essential follow-up studies, constituted a *sine qua non* in a metropolitan tuberculosis program. On the maps, fashioned by the interwoven and mutually provocative influences of congestion, poor housing, racial trends and lowered economic status, "islands" of tuberculosis mortality and morbidity stood outlined with almost geographic clarity, islands unfortunately, as might be expected, most difficult of access through any medium at our disposal.

Notwithstanding the fact that our clinics were located, designedly, in the areas of high mortality, the total response to routine clinic procedure proved inadequate in the face of the extent and urgency of the problem. Despite propaganda, vigorous contact examinations, follow-up into the homes, it was felt that we had no real anchorage in the "red-pin archipelago" and, as a consequence, the majority of the cases, as reported in the clinics, continued in the moderately and far advanced brackets when first seen. The reefs of passivity, ignorance, deplorable living and subhuman hygiene hindered any attempt at sustained health traffic. In short, despite our best efforts, including exhibits, institutes, drives and extensive refresher courses for the neighborhood physicians, we saw only symptoms and symptoms in the "islands" almost invariably meant pronounced disease.

The pronounced disease, the futility of our attempts to strike at early tuberculosis in the socially and economically submerged areas worried and exercised us. The archipelago of red pins became a *bête noire*. Epidemiological considerations demanded that the residents of the areas in question be examined *en masse*. Since, however, the residents, indifferent to epidemiology, could not be induced to come to the clinic, the only alternative left dictated that the clinic, in one form or another, should go to them. We tried and failed and tried again. Block-by-block drives, survey from door to door, including physical examination in the home, having proved ineffective, we finally came to the conclusion that mass roentgenological examination, X-ray on wheels that took the survey to the doorstep, seemed the only solution.

In the pre-photoroentgenographic era, however, X-ray on wheels projected against the cost of the 14 x 17″ film seemed an illusory objective. Nevertheless

[1] From the Municipal Tuberculosis Sanitarium, Chicago, Illinois.

and in view of the basic values at issue, we undertook the attempt. With the generous, even enthusiastic assistance of the Tuberculosis Institute of Chicago and Cook County (a branch of the National Tuberculosis Association) a self-contained, completely equipped, mobile unit, mounted on a one and one-half ton, balloon-tired truck with van body, was designed and constructed. The unit, the first of its kind in the X-ray field, still in use though limping toward obsolescence, included three dressing rooms, a dark room, lead-lined cabinets for storage, four heaters, a ventilating fan and a 200-foot cable for the power connection.

At the start, and in fact throughout most of our early work, in an attempt to dilute the film expenditures toward some degree of compatibility with the budget, we used the tuberculin screen, an experiment handicapped by an unduly high reactor incidence in the districts under survey and not too profitable as a whole. Deviating, *per necessitatem*, from our primary objective we oriented our case-finding toward the high schools, colleges and small employee groups, kept the mobile X-ray unit in more or less continuous service, with the result that, during the years 1937, 1938 and 1939, 167,345 persons were tuberculin tested and 23,532 reactors X-rayed.

Though the campaign, on the whole, hardly justified the expenditures, nevertheless we persisted in our ambulatory X-ray experiments, hoping meanwhile that some new medium or technique would bring mass community X-ray survey within the domain of economic possibility. With the advent of photoroentgenography and its amazingly fast development, the hope was soon realized. Made cognizant of DeAbreu's experience through some of his earlier articles in foreign journals, we followed his work in Rio de Janeiro and watched very closely the development of the miniature film in this country. To this end we sent representatives to canvass the possibilities, discussed his pioneering experiences with Lindberg and a little later found ourselves extremely interested in Potter's collaboration with General Electric toward the development of the 4 x 5″ film, an epochal, revolutionary effort to which the clinics of the Municipal Tuberculosis Sanitarium contributed, as test material, some scores of patients representing different pathological types and varying physiques.

Convinced by personal observation that the 4 x 5″ photoroentgenographic unit, as we saw it in its day-to-day development, represented from the viewpoints of economy and efficiency the answer to our need, we contracted for this equipment in January, 1940. Detroit, we believe, got the first unit produced, our institution the second or third. Some months later, encouraged by our immediate survey results, eager for fresh pastures and results still better, we ordered a second unit, the 35 mm. apparatus. We found, however, that enthusiasm had outpaced the realities. Due to budgetary and personnel considerations, and even with the help of the Institute, we found we could operate only one unit at full efficiency. After a period, therefore, in which we used both units simultaneously and alternately, we summarized our experience and gave preference to the 4 x 5″ equipment. Since early 1940, working mainly with the

4 x 5″ unit, using the 35 mm., paper film and fluoroscopy for comparative study, the mobile X-ray division of the Sanitarium has photoroentgenographed 202,552 persons, with a total net gain of 5,596 new cases found.

RELATIVE VALUES OF THE VARIOUS METHODS

As in the course of the work we have had experience with the 14 x 17″, 4 x 5″, 35 mm., paper film and fluoroscopy, the question naturally arises as to our concept of relative values. By way of broad preface we might state that all of the procedures have a place, that any one of them is immeasurably superior to the routine case-finding methods accepted as standard even as late as a decade ago. In general, however, we agree with Dunham, Potter, Christie, DeLorimier and others that, from the point of view of adaptability, diagnostic trust and efficiency, the stereoscopic 4 x 5″ film is the best method developed for mass survey.

In a paper of this scope it is impractical to embark on a graded evaluation of all the measures. Those interested in more specific details are referred to DeLorimier's exhaustive article *Mass Roentgenography of Chest,* in the April, 1942 issue of Radiology. In a very interesting tabulation DeLorimier places the 4 x 5″ stereoscopic film first for mass study, second for individual case observation. His table, as he grades the different methods, brings out very clearly the distinctive radiological attitudes as between individual and mass film studies and emphasizes the opinion of many workers that restriction of the field of the image and condensation of detail are advantageous for rapid and continuous interpretation in volume.

With one element in DeLorimier's "Mass Study Column," the position of the 35 mm. stereoscopic film as second, we are inclined to disagree. From the first we had felt that the 35 mm. image was too small. The elimination of the film perforations, which seemed an imminent and necessary innovation, would, we hoped, make for better and more exact interpretation. The perforations were eliminated in due course but the resultant increase in image size proved, in our opinion, too slight to dilute the intense overconcentration which still responded to magnification with some degree of distortion and an excess of grain. Notwithstanding this primary disappointment we still felt roll film, in the interests of speed and expediency, held distinct possibilities in mass X-ray survey. As early as 1941 we approached two of the equipment houses on the matter, expressed our belief that a roll film intermediate in size between 35 mm. and the 4 x 5″ would meet certain survey requirements.

Though somewhat discouraged by the lack of immediate response, we had kept this thought in mind, felt it thrive and stir in the light of experience and, when a strip of 70 mm. film came to our attention some weeks back, we were immediately and fundamentally interested. The contrast and detail in the specimen images looked so promising both to the naked eye and through the viewer that we were at once intrigued with the idea of making a comparative study of the 4 x 5″ and the new film. After considerable preliminary groundwork the arrangements were made, the mechanism set up for the photoroent-

genographic examination of 1,713 employees of an industrial plant with both types of equipment.

PROCEDURE

With identical technique, the same kilovolt peaks, same milliamperage, same target-to-screen distance, the time controlled by the Morgan timer, all films, as the employees were routed successively before the two photoroentgenographic units, were taken stereoscopically.

Regarding interpretation, the committee system was used. Needless to say, control reading of several thousand films, though it has its disadvantages, tends to explore and correct the individual trend which seems to be the inalienable privilege and universal right of every one who spends his days in front of a viewer. In the evaluation of a new medium the correction of trend and personal equation seemed important, hence the committee was composed, in the present instance, of two interpreters with the writer as umpire in the disputed cases and final readings. As the first step, all films, both 4 x 5″ and 70 mm., were read separately by the two physicians both of whom have had special training in miniature interpretation. Four sets of record cards (a card for each interpretation) were used and the examination was so conducted that neither of the interpreters, at the time of interpretation, had knowledge of the other's result.

As the work proceeded the statistician checked the results, held out all cards, either 4 x 5″ or 70 mm., on which the interpreters failed to agree, and charted the divergent findings on a control card designed to be used later as the basis for the joint and final reading.

STATISTICIAN'S CONTROL CARD

Name ______ John Doe ______ X-ray No. ___100___
Age ___53___ Sex ___M.___ Color ___White___

4 x 5		70 mm.	
Diagnosis		Diagnosis	
Dr. A.	Min. L.A. R-1	Dr. A.	Negative
Dr. B.	Suspect R-1	Dr. B.	Negative
Joint	Minimal R-1	Joint	Negative

14 x 17 Film: Yes ___x___ No ______
Final Diagnosis ______ Minimal ______ Location ___R-1___
Predominant pathology ______ Fibro-calcific ______
Pleurisy ______
Primary ______ Negative ______
Non-Tbc. condition ______ Scoliosis ______
Remarks: ______

In the joint and final readings at which the writer assisted, the three members of the committee working in unison, with the complete data of each employee as the unit, first read the 70 mm. and 4 x 5″ films successively, then correlated the results by individual application of the 70 mm. reading against the 4 x 5″ reading. In every disputed case a 14 x 17″ film, previously ordered, played its part in the final or agreed diagnosis.

EQUIPMENT

For basic X-ray equipment we used two General Electric 200 milliampere machines, equipped respectively with the standard General Electric 4 x 5" photoroentgenographic attachment and the new 70 mm. apparatus (Fairchild camera, 1.5 coated lens of $4\frac{5}{8}$ inch focal length). Both machines used the General Electric photo-timer (Morgan-Hodges principle).

By way of viewing mechanism, we employed the General Electric orthostereoscope for the 4 x 5" films, for the 70 mm. films a stereoscopic magnifying viewer by the same company which, though still in the later experimental stages, gave excellent results including a depth perspective of surprising clarity. The processing was competently and rapidly effected by the Smith-Fairchild unit, a model consisting of a light-tight solution tank approximately 5" x 11" x 5", a compact arrangement which held the entire roll of film and developed the 400 negatives in forty-five minutes. The Fairchild-built, motor-driven drying unit (equipped with a heating element) equally expeditious and efficient, rather intrigued the technicians by drying the 100-foot roll in about twenty minutes.

GENERAL IMPRESSIONS

All films were viewed stereoscopically. As the work went on the writer, sitting in with the interpreters, attempted to summarize current impressions. One of the readers liked both types of film almost equally well but professed a mild preference for the 4 x 5" (stereoscopic pair) and a slightly increased sense of security in the detection of minimal lesions. The second interpreter acknowledged a definitely greater diagnostic trust in the 4 x 5" films and it was his feeling that the 70 mm. was about 75 to 80 per cent as efficient. The writer, after observation of long series of films, felt rather inclined to the belief that, from the standpoint of gross survey, there was very little choice one way or another. After all, the difference in actual image size is not so great, $2\frac{1}{2}$ x $2\frac{7}{8}$ inches as against $3\frac{3}{4}$ x $4\frac{3}{4}$ inches. Furthermore, the difference in size, such as it was, seemed to the writer to be neutralized by a more precise stereoscopic projection on the part of the 70 mm. viewer. This impression, of course, may be entirely subjective. Individual reaction to photoroentgenographic stereoscopy varies within wide limits and the qualities of the respective images, in the present instance, were close enough that an observer interested in the potentialities of roll film could easily be swayed. In any event, and from the standpoint of conventional physical measurements, though such are by no means indicative of the degree of diagnostic trust, the 11 per cent reduction in resolving power noted for the 70 mm. films in comparison with the 4 x 5" films seems to corroborate the interpreters' impression rather than the writer's.

RESULTS

In analyzing the results it may be simpler, perhaps, to start with the final readings, that is, the interpretation agreed upon by the three members of the committee after a joint study of all the films, including the 14 x 17" films. The detail is given in table 1.

Consideration of table 1 reveals that, in the final review, 1,653 of the 1,713

cases, or 96.5 per cent, were adjudged normal. Thirty-seven, or 2.2 per cent, were read as showing reinfection type tuberculosis, a percentage considerably higher than the average of 1.0 per cent encountered in our industrial work and due, we think, to a liberal employment policy and a pressing need for help on the part of the plant in question. The relatively low number of minimal lesions and suspects is explained by the fact that a considerable number of films originally classed in one or both categories were weeded out through successive consultation and again through the mutually corrective influence of three types of film. To quote an instance, in the preliminary readings one of the physicians read 2.1 per cent suspects for the 4 x 5″ films against 2.0 per cent for the 70 mm. films, the other physician a higher but still mutually comparable ratio for both types of film.

TABLE 1

Final diagnosis

	NUMBER	PER CENT
Minimal	18	1.1
Moderately advanced	15	0.9
Far advanced	4	0.2
Total reinfection	37	2.2
Suspects	23	1.3
Normals	1,653	96.5
Total	1,713	100.0

THE COMPARATIVE STUDIES

Before we start the discussion of the comparative analysis, we must stress again the question of trend, a scientifically distasteful subject, usually avoided, yet sufficiently obvious in committee interpretive work on any large scale. In reality there is nothing too discouraging in the concept of trend. No two people, even of equal intelligence, read exactly the same significance into a long newspaper paragraph and no two people see an accident or scenic panorama exactly alike. Why then, if we accept a margin of subjective variation for the ordinary, visual phenomena, must we demand an utterly scientific objectivity in the interpretation of a design as intricate and illusive as the X-ray image.

In the present study the question of individual leaning was exemplified by an index of agreement of 93.6 per cent for the 4 x 5″ film considered by itself, as against 94.9 for the 70 mm. film, a differential of 1.3 per cent, interesting rather than significant and not to be construed as a factor in favor of the 70 mm. film. Incidentally, and as may be supposed, the failure to agree in both instances centred almost entirely in the suspect and the minimal group, mostly the suspects. As the next step in the analysis and applying the 4 x 5″ films against the 70 mm. films, the index of agreement on the first reading was figured at 89.9 per cent.

In other words, the total primary failure when the films were crossed against each other was not so very much more than the failure due to the personal variation when the two types of films were read separately. In the later joint readings the 89.9 per cent grew appreciably and the 4 x 5″ and 70 mm. films agreed in 1,672, or 97.6 per cent of the cases, a disparity which is broken down as to detail in table 2.

Considering table 2 and speaking from the point of view of a survey, the discrepancy in the 6 cases read diversely as minimal and suspect, even the 2 cases read as moderately advanced on one film, suspect on another, is not important. As all our cases, both suspect and diagnosed, are immediately followed up by the clinics, the suspect, for purposes of supervision, assumes equivalent importance and receives equally conscientious study, including sputum analysis, serial X-ray films, periodical physical examination. In short, more and more partial to the idea of the photoroentgenogram as merely a screen, somewhat indifferent as a result to fine interpretative shades, we fish in the stream, sort and weigh in the clinics.

TABLE 2

Failure of agreement—4 x 5″ and 70 mm. films

Read suspect 4 x 5″	—negative 70 mm.	17
Read suspect 70 mm.	—negative 4 x 5″	14
Read minimal 4 x 5″	—negative 70 mm.	2
Read minimal 4 x 5″	—suspect 70 mm.	4
Read suspect 4 x 5″	—minimal 70 mm.	2
Read moderately advanced 4 x 5″	—suspect 70 mm.	1
Read suspect 4 x 5″	—moderately advanced 70 mm.	1

Disregarding, then, the discrepancy between suspect and minimal, we come to the really significant item in the table, the 2 minimal cases which, at first sight, seem to have been uncovered by the 4 x 5″ and missed by the 70 mm. films. In the preliminary reading, both interpreters classed the cases as negative in the 70 mm. films. On the 4 x 5″ films, on the other hand, both cases were classed as minimal by one physician, both as suspect by the other. In the final consultative reading, however, comparing all films including the 14 x 17″, one of the cases was classed as minimal and one negative. In other words, one minimal case uncovered by the 4 x 5″ film would have been lost if the 70 mm. film alone had been used.

ABSTRACT OF TABULATIONS

The working data and detailed tabulations are much too voluminous for inclusion in a paper of this kind and are being arranged for publication in one of our Bulletins. Table 3, extremely condensed, gives some idea of the main elements in the comparative study.

Considering the tabulation, of the 36 cases read as reinfection tuberculosis on the 4 x 5″ films, 29 were read the same on the 70 mm. films, 5 as suspect and 2 as normal. In view of what already has been said and from the standpoint of

a survey, the 2 cases read as normal constitute the differential and this has already been discussed in connection with table 2. Twelve of the 32 cases classed as suspect on the 4 x 5″ films were so confirmed by the 70 mm. films and 17 were classed as normal. Of the 31 cases read as suspect on the 70 mm. films, 12 were so confirmed on the 4 x 5″ films, 14 read as normal and 5 as reinfection tuberculosis.

Regarding the tabulation as a whole, centering attention on the suspects, the 5 cases so classed on the 70 mm. films and diagnosed reinfection tuberculosis on the 4 x 5″ films are not too significant from the point of view of mass work. The reason for this has already been stated. *If it is to serve any purpose,* photoroentgenographic survey should be supplemented with follow-up and if the follow-up postulates equal primary supervision for suspect and diagnosed cases, the disparity from the angle of ultimate case-finding is not important.

Some further detail is furnished by table 4, which represents the final consultative interpretation (three readers) crossed against the joint 4 x 5″ and 70 mm. film readings and controlled by the 14 x 17″ films.

TABLE 3

4 x 5″ films crossed against the 70 mm. films—joint reading

INTERPRETATION 4 x 5″ FILM	INTERPRETATION 70 MM. FILM			TOTALS 4 x 5″ FILM
	Reinfection	*Suspect*	*Normal*	
Reinfection	29	5	2	36
Suspect	3	12	17	32
Normal	0	14	1,631	1,645
Total 70 mm.	32	31	1,650	1,713

Table 4 sustains the previous tendencies. Of the 37 cases classed as reinfection type tuberculosis in the final consultative reading, 35 had so been read on the 4 x 5″ films, 2 as suspects as against 31 reinfections, 5 suspects and one normal in the 70 mm. films. Again and from the point of view of screening, the differential of 10.8 in diagnosed cases was unimportant as those that escaped the finer net of diagnosis were meshed as suspects. Furthermore, since the one case read as normal on the 70 mm. film, as reinfection on the other film, was finally classified minimal, right upper, fibro-calcific type, the loss on the part of the 70 mm. film can hardly be called significant.

In review and in consideration of all the tables, it would seem that, although the two methods are almost even as a screening mechanism, the 4 x 5″ film, a shade better in gross characterization and much better in exact delineation, remains the finer diagnostic instrument. Based on the relative screening qualities, a question naturally arises. For survey purposes, is the finer instrument necessary? In view of the relative costs and the nearly equivalent efficiency ratings, is the 70 mm. destined to supplant the 4 x 5″ film? We do not think so. In the first place, in terms of miniature film cost against the background of personnel and general survey expenses, the exposure charge is relatively in-

significant and the question of whether we have to pay one and one-quarter cents, three cents, or five cents per processed exposure should not be allowed to become decisive in the choice of equipment. In the second place, and due to its intrinsic qualities, the 70 mm. film cannot supplant the 4 x 5" or even seriously threaten its position. It does not have to supplant and there is no need for threat.

The 70 mm. film has its own place and its own individuality. Everything in its mechanical structure proclaims that it comes not as an usurper but as an

TABLE 4

Final interpretation by whole committee

FINAL INTERPRETATION	4 x 5" FILMS JOINT READING		70 MM. FILMS JOINT READING	
	Number	Per cent	Number	Per cent
Reinfection:				
Agreement	35	94.6	31	83.3
Changed from suspect to reinfection	2	5.4	5	13.5
Changed from normal to reinfection	0		1	2.7
Total	37	100.0	37	100.0
Suspect:				
Agreement	16	69.6	17	83.9
Changed from reinfection to suspect	0		1	4.4
Changed from normal to suspect	7	30.4	5	21.7
Total	23	100.0	23	100.0
Normal:				
Agreement	1,638	99.1	1,644	99.5
Changed from reinfection to normal	1	0.1	0	
Changed from suspect to normal	14	0.8	9	0.5
Total	1,653	100.0	1,653	100.0
Total				
Agreement	1,689	98.6	1,692	98.8
Disagreement	24	1.4	21	1.2
Total	1,713	100.0	1,713	100.0

auxiliary, that the two photoroentgenographic modes are mutually adaptable and complementary, that each rounds out the other and that both together fill in the outline of the mass X-ray concept. "A program big enough for the 70 mm. film should also be able to afford the 4 x 5" and the simultaneous use of both types of equipment against diverse objectives represents the ideal." Everything is enclosed in the objective and the choice is inherent in the aim. What are we working toward, how fast do we have to work and how delicately? On the answer depends the decision as to what type of mechanism we should use.

To us, as during the course of the present study we have come to see it, the 4 x 5″ and the 70 mm. films represent two highly individualized processes, two different technical personalities, oriented toward a future in two different fields. The fields, of course, adjoin, even overlap and the division entirely empiric, tentatively outlined here, merely suggests an ideal. Short of the ideal which is rarely, if ever, attained anywhere, the rôles are sufficiently elastic to stretch to expediency, the results of either type of equipment in any type of survey work sufficiently good to be classed as acceptable against the necessities of the situation. With these reservations in mind, using the basic differences of function as the guide, an attempt to outline broadly the respective sphere of usefulness may be justifiable.

THE FIELD OF THE 70 MM. FILM

The advantages and disadvantages of roll-type film of the size and type in question define the province of the 70 mm., a province which though extremely important is nevertheless limited, with the factors that create the importance specifying the limitations. Speed against volume, with the sacrifices that speed and volume demand, spell the story. The automatism of the roll mechanism, the ease, the interchangeability of loading, the simplicity, the rapid, uninterrupted operation, the extremely fast developing, the acceleration of interpretation through the winding viewer, the general accentuation of tempo and a screen fine enough for the purpose define the qualifications of the 70 mm. equipment.

Given the qualifications, whither do they point? Toward the sphere of massive, continuous survey if we read correctly, toward the expansive, photoroentgenographic program where screening rather than diagnostic precision, volume rather than individual study, discovery rather than delineation are the prime aims. In line with the aims and influenced by the qualifications as we see them, we are inclined, as a result of our observations, to visualize the field of the 70 mm. film as (*a*) military screening, (*b*) large industrial surveys, (*c*) progressive surveys in metropolitan centres, (*d*) mental hospitals and other institutional examination, (*e*) any massive, unbroken program against a constant objective where summaries rather than daily analyses, the report rather than the chart are the prime considerations.

What does all this leave for the 4 x 5″ film? On first consideration, according to this rather arbitrary division of ours, it would seem as if the 70 mm. film had the lion's share. Such, however, is actually not the case. Though the volume factor of the 70 mm. film is important, the volume of the varied functions of the 4 x 5″ film is as great or greater and the summated values even more important.

THE FIELD OF THE 4 x 5″ FILM

In the 70 mm. films we sacrificed specialization for speed, in the 4 x 5″ films we reverse the process and stress individualization. By individualization we mean not only a closer study of the individual film but, in addition, a much

more intimate group-relationship, an orientation toward more restricted purposes and areas wherein, broadly speaking and as regards processing in detail, the day's work should finish with the day.

To illustrate, let us suppose a metropolitan program which uses both types of equipment simultaneously. In such a program, while the 70 mm. equipment concerns itself chiefly with large industrial plants, the 4 x 5" film could be used for plants of 200 or less, for sweatshop and lodging house surveys, special grade examination in the schools and for periodic survey of such groups as food handlers, restaurant employees, etc. Outside the metropolitan areas, in restricted or semi-continuous programs which use only one unit, the preference would seem to deviate toward the 4 x 5" equipment. For interrupted work in small groups, roll-film with its 400 negatives is cumbersome and confusing. For such state or county traveling units, for instance, as are designed to offer photoroentgenographic survey to tuberculosis bodies operating in rural areas and small towns, the 4 x 5" film would seem to be preferable.

THE UNOFFICIAL OR ADJUVANT PUBLIC HEALTH FUNCTION OF THE 4 x 5" FILM

In addition to its inherent meaning as a survey instrument, the 4 x 5" film, through its adaptability to certain allied activities that interdigitate with the preventive program, shows promise of continued and accrescent influence as a public health catalyst. In this connection one thinks particularly of the 4 x 5" equipment as the medium for the admission X-ray films in general hospitals, for the preplacement examinations in industrial plants, for the "graduation chest film" which, sooner or later, will accompany every grammar school graduate into high school, every high school graduate into college or industry. This and the many similar developments inextricably bound up in the photoroentgenographic lineaments of the coming public health picture inevitably bring us to the future. What of to-morrow?

FURTHER DEVELOPMENTS

What does the future hold for photoroentgenography, not for this type or that, but for the mode as a whole? Unprecedented growth according to the indication; expansion to the full, to the limit of the mechanical possibilities and the perimeter of the tuberculosis problem; an expansion therefore necessarily rather revolutionary, total surveys in every metropolitan centre, photoroentgenographic units in every municipality, federal units, state units, county units, the gypsy X-ray van for rural areas, the X-ray river boat for the bayou country; hand in hand with all this and as its logical derivative, the concomitant advance in the legislative pattern, mandatory hospitalization, the photoroentgenogram pinned to the barber's license, the student's diploma, the teacher's certificate and, last but not least, the "Constable Carry-all" for compulsory total survey of slum areas with steep tuberculosis mortality!

Hitlerian! Not at all! Obligatory photoroentgenography aligned to the necessities, as a measure of social protection against ascertained risks, lies well within the framework of a democracy conscious of itself, aware of its purposes

and awake to its responsibilities. Totalitarianism, Fascism, tyranny! Where? How? The screen is certainly less obnoxious than vaccination, definitely less painful than income tax and the most conscientious of conscientious objectors can hardly allege that the momentary fluorescence is, in any way, conducive to the "March melancholics," the anxiety neurosis, the sense of depletion or the fear of a sore arm.

All very fine but will the public accept it? Definitely! The overwhelming psychological response, the swift and generalized acceptance indicate to those in the work that the public has come not only to expect but to demand that the health and welfare guarantees implicit in photoroentgenography be exploited to the full. Whence the demand? Is it spontaneous, chance-birthed, a mushroom growth in a casual dew? By no means! Based on sound publicity principles, it was planned that way. Photoroentgenography represents the long-sought pearl in the crown of propaganda and the National Association, the U. S. Public Health Service and, within their limitations, such institutions as ours have turned on all the lights in the show-case.

The results! As photoroentgenography energizes propaganda and propaganda engenders demand, in Chicago, and doubtless to a similar degree elsewhere, the available mobile facilities are booked ten months ahead. The way it looks and in view of the equipment at our disposal, we overlit the show-case.

THERAPY

Possibly all of us, to some extent at least, will agree to the evolution of the legislative and public health patterns as mass X-raying is projected against its possibilities. Is the massive case-finding inherent in the future of photoroentgenography destined to influence our present standards of treatment? Several of the writer's colleagues think so. In their opinion, the insistent cry for beds, beds, more beds, will echo against the growing hills of case-finding, fall back in the lap of the economic realities, as a plea for a combined sanatorium-clinic home-care plan, including BCG, extramural pneumothorax (bed-side as necessary), close home supervision, basic nursing service, pay-as-you-go or partially subsidized group homes for infectious workers, cases of benignant isolation such as advocated by this institution twenty years ago, such as at present operated as "night-sanatoria" in Russia.

THE FUTURE IN TERMS OF TECHNOLOGICAL ADVANCE

Finally, as to the thing itself, the genius of the lamp, the *deus ex machina!* The technology of photoroentgenography, what further does *that* have to offer? Much! The radiologist and the physical scientist who have given, will continue to give. While there is no doubt about the gift, the manner of giving must, for the present at least, remain problematic. As to the form and size of the film, and the purely operative mechanism, the 4 x 5″ and the 70 mm. film, each adequately representative in its field, will probably remain substantially as they are. The advances as they materialize will come in lens, screen, camera structure, photographic chemistry, truck design and fluoroscopy.

In fluoroscopy, particularly, the one survey element that has lagged, the one medium accessible to the private physician, advances of moment may be expected. Let us hope that the expectations are realized. To-day, the physician in general practice has no place in the survey picture and without his active participation no program is complete. To bring him in, to gain his participation inside the wide circle of survey activities, the public health man again calls on the scientist, this time for fluorescent amplification, a brighter screen, a wash-out of "dark adaptation," a cheaper instrument, safety, a problem perhaps more intricate than any the scientists have surmounted, yet doubtless with an answer. Will they answer it?

In thinking along these lines, Hilleboe wishfully runs the scale of the possibilities, the inconoscope, the Langmuir image tube, the multipactor tube, and suggests, in his conclusion, that the evasive fluorescent amplification, the will o' the wisp of the radiologist, may soon become a reality. We hope and we believe. We cannot help ourselves. Since DeAbreu we have witnessed and wondered. Enthralled by the magic of the men of science we look from the photoroentgenographic images to the "conjure" hat and back again, speculate "what next," sink present, past and future into a common wishing well and expect endlessly. It's ever thus. Those who have seen the miracle are confirmed forever in the faith, and if the incredible procession of events has pyramided optimism to the clouds and tinted enthusiasm with credultiy, are we to blame?

SUMMARY

Using identical technique and the Morgan timer, 1,713 industrial employees were subjected to photofluorographic examination by both the 4 x 5" and the 70 mm. types of apparatus. All films were taken stereoscopically. For interpretation the committee plan was used. For viewing, the General Electric orthostereoscope was employed in the case of the 4 x 5" film; for the 70 mm. film a new stereoscopic magnifying viewer gave excellent results.

Of the 1,713 cases, 37, or 2.2 per cent, were classed as reinfection type tuberculosis on the final joint readings. In the early readings, before both types of films were crossed against each other for the final diagnosis, 36 cases had been classed as reinfection tuberculosis by the 4 x 5", 32 by the 70 mm. films. Five cases classed as "suspect" by the 70 mm. films were read as minimal on the 4 x 5" films. As all cases, both suspects and minimal, are taken under immediate observation by the clinics, the disparity between the minimal and suspect cases is not significant from the point of view of screening.

In the final results, one case diagnosed as minimal by the 4 x 5" was missed by the 70 mm. film. As a result of the examinations we concluded that, while the 4 x 5" film remains the finer diagnostic instrument, the two photofluorographic modes are practically equivalent for screening purposes. For rapid and continuous mass survey, the 70 mm. film seems preferable. For smaller and more compact studies, the 4 x 5" film seems to be the method of choice.

SUMARIO

A 1,713 empleados industriales se les hicieron exámenes fotorroentgenográficos con los aparatos de 10 x 12.5 cm y de 70 mm, utilizando una técnica idéntica y el cronómetro de Morgan. Todas las películas se obtuvieron roentgenoscópicamente, utilizando para interpretación el plan de la comisión. Para estudio se empleó el ortoestereoscopio de la General Electric en las de 10 x 12.5 cm y en las de 70 mm dió magnífico resultado un nuevo estereoscopio de aumento.

De los 1,713 casos, 37 (2.2%) fueron clasificados como de tuberculosis tipo reinfección en las lecturas combinadas definitivas. En las primeras lecturas antes de comparar ambos tipos de películas para el diagnóstico definitivo, 36 casos habían sido clasificados como de reinfección con las películas de 10 x 12.5 cm y 32 con las de 70 mm. Cinco casos clasificados como "sospechosos" con las de 70 mm fueron considerados como mínimos con las de 10 x 12.5 cm. Como todos los casos, tanto sospechosos como mínimos, son objeto de observación inmediata por los clínicos, la discrepancia entre los casos mínimos y sospechosos no tiene importancia desde el punto de vista del despistaje.

En los resultados definitivos un caso diagnosticado como mínimo con las películas de 10 x 12.5 cm pasó desapercibido con las de 70 mm. Como consecuencia de estos exámenes dedújose que aunque el aparato de 10 x 12.5 cm continúa siendo el más delicado para el diagnóstico las dos técnicas fotorroentgenográficas vienen a ser equivalentes para fines de despistaje. Para encuestas colectivas rápidas y continuas el de 70 mm, parece preferible, mientras que para estudios más pequeños y compactos el aparato de elección parece ser el de 10 x 12.5 cm.

REFERENCES

CHRISTIE, ARTHUR C.: Evaluation of methods for mass survey of the chest, Am. J. Roentgenol., 1942, *47*, 76.

DEABREU, MANOEL: A situacao atual da roentgen-fotografia na profilaxia da tuberculose, Rev. brasil. de tuber., November-December, 1938, *8*, 43.

DEABREU, MANOEL: Collective fluorography, Med. & Surg. Soc. of Rio de Janeiro, July, 1936.

DELORIMIER, ALFRED A.: Mass roentgenography of the chest for the United States Army, Radiology, 1942, *38*, 462.

HILLEBOE, HERMAN E., AND MORGAN, RUSSELL H.: Mass Radiography of the Chest, Year Book Publishers, Chicago, 1945.

TICE, FREDERICK: The miniature X-ray film in the "total survey," J. A. M. A., October 12, 1940, *115*, 1254.

CUTANEOUS REINFECTION IN PULMONARY TUBERCULOSIS[1]

C. FLOYD, H. A. NOVACK AND C. G. PAGE

In Koch's (1) tenth series of experiments, following his discovery of the tubercle bacillus, the first recorded group of reinfections was described. For two months he fed rats exclusively on bodies of tuberculous animals and followed this with intraäbdominal inoculations of cultures obtained from an ape. In later experiments he proved the marked difference in reaction to intracutaneous inoculations of viable tubercle bacilli in tuberculous and nontuberculous animals.

Trudeau (2) found that, when animals were inoculated with virulent tubercle bacilli, those that had previously been vaccinated with tubercle bacilli had their lives prolonged as compared with animals that were unvaccinated, the infecting dose being uniform.

Nichols (3) continued along similar lines studying the histological differences in Belgian hares, some vaccinated and others not; the superimposed infection consisting of an intravenous inoculation of .0001 g. of a broth culture of R1. The early response of the lungs at autopsy in the vaccinated group was that of marked pulmonary congestion, speckling with large and small hemorrhagic spots and numbers of minute, translucent tubercles plainly visible to the naked eye. At the end of thirty days, the lungs were practically free of tubercle bacilli and the parenchymal abnormalities were much less in evidence.

In the controls, on the other hand, there was little to denote pulmonary pathological changes up until a lapse of two and one-half weeks. At this time tubercles were readily apparent and developed rapidly, undergoing fragmentation and caseation, with numerous bacilli at their centres and fibrous tissue beginning to form about their periphery.

In a series of observations on tuberculous superinfections in rabbits, Schwabacher and Wilson (4) failed to produce, in the lungs, progressive pulmonary disease with virulent bacilli. Failure in this regard was also obtained in other animals. These negative results lead to the conclusion that reinfection or superinfections, experimentally produced in laboratory animals, could throw little light on the pathogenesis of tuberculosis in man.

Krause and Willis (5) in their experimental studies on reinfection tuberculosis have shown that repeated infections will produce violent acute reactions at first, but soon become chronic and have little tendency to spread; primary infections by similar doses progress leisurely but irresistibly to a progressive form of the disease.

Willis (6) noted the marked retardation of the spread of tubercle bacilli inoculated into the skin of guinea pigs made allergic or immune by previous infection with tubercle bacilli. The immune or already infected animal appeared to fix the bacilli at the point of introduction for at least four or five days, preventing wide-spread dissemination by means of the rapid inflammatory processes

[1] This study was sponsored by the Boston Tuberculosis Association.

of the allergic reaction. In the normal animal bacilli can be found 4 to 5 cm. distant from the point of inoculation in twenty-four hours, whereas in the immune animal such transit requires a little less than three weeks.

Lurie (7), in his extensive researches on mononuclear phagocytosis, has given a detailed account of the activities of these cells in normal animals and in those with reinfection tuberculosis. As is the phagocytic response to tubercle bacilli, so also is the response of tuberculous rabbits and guinea pigs greatly accelerated to nonspecific substances as well. Mononuclear cells, derived from tuberculous or vaccinated animals, exhibit greater phagocytic capacity *in vitro* for carbon particles, staphylococci or tubercle bacilli than do the cells of normal animals; their phagocytic capacity for tubercle bacilli depends upon the virulence of the vaccinating or infecting bacillus. The less virulent the organism, the less phagocytic the activity of the cells. In another publication, Lurie (8) has demonstrated the means by which bacilli of reinfection are effectively fixed at the portal of entry. In studying the differences in local reactions of guinea pigs and rabbits, the well known fact that the more highly sensitized guinea pig shows a much more severe reaction to reinfection inoculation with tubercle bacilli or even to nonspecific substances was demonstrated to be due, at least in part, to mechanical differences in the species reactions. This sensitization has been correlated with the degree of allergy; the greater the allergic response, the greater the reaction to sensitivity in the animal and the more prolonged the fixation of bacilli at the area of inoculation. Mechanically this is brought about by profuse exudate in the guinea pig, coagulation of the exuded plasma, and mainly thrombosis of the adjoining lymph vessels quickly shutting off the focus of reinfection.

Soper (9), following the ideas of Koch's early experiments and basing his work on that done by Nichols, mentioned above, used vital staining methods in an attempt to study the effects upon liver tissue of reinfected rabbits. He concluded that the liver of a rabbit possessed a great degree of immunity to a second virulent infection with bovine tubercle bacilli, and that the course of the disease was practically identical with that produced in the rabbit's lung. The type of cell concerned in the second infection reaction is the same as that concerned in the reaction to the primary infection, the difference being one of degree and rapidity of production.

Controversial evidence has now for some time been collecting on the value of cutaneous tuberculosis in its modifying influence on other concomitant manifestations of the disease. Much clinical work has been done on the subject of immunity or resistance to phthisis as a result of accidental or deliberate involvement of the epidermis with the tubercle bacillus. Among certain observers it has long been an axiom that wherever lupus was present pulmonary tuberculosis very rarely occurred subsequently; and where it was acquired in a case of preëxisting pulmonary tuberculosis, the course of the disease was materially modified. Such cases have come to the attention of the writers, but they have been too few to warrant the drawing of any conclusions.

In 1937 Kutschera-Aichbergen (10) cited many patients with advancing pulmonary tuberculosis who began to improve promptly, and did so to a marked

degree, soon after their skin was infected therapeutically with tuberculosis. He distinguishes clearly between the harmless therapeutic and dangerous prophylactic use of living cultures.

Tufts' (11) review of the literature on this subject led him to summarize as follows: "It would seem that the concensus of opinion is in favor of a distinct relationship between the skin and the processes of immunity; that in allergic diseases, cutaneous antibody formation may be a menas by which immunization of the entire body is brought about. The point of controversy seems to center upon the question as to whether in certain allergic and infectious diseases, the skin can form specific antibodies."

In spite of the evidence that seems to point to the skin as an immunological organ, Michelson (12) concludes that there are no proofs of the oft repeated statements that cutaneous tuberculosis raises the resistance of the individual to internal tuberculosis.

METHODS

It will be recalled that Koch's early reinfection experiments were based on feeding infected material; Trudeau used virulent cultures. In the present work on reinfection tuberculosis in guinea pigs, pulmonary lesions were established by feeding after the method of Calmette (13). By this means parenchymal tuberculosis, as is often seen clinically, is readily established and the initial infection of the animal body is not nearly so generalized as occurs in intravenous inoculations.

A virulent strain of H37 was used both for ingestion and cutaneous inoculations, and frequent animal passage allowed no drop in its infectivity in producing ingestion tuberculosis. One cc. of a suspension of tubercle bacilli containing .01 mg. by weight was the infecting dose and this was repeated for five consecutive weeks. The inoculum was injected into the stomach through a No. 8 French catheter and the tube irrigated while in place with sterile water.

The amount of infecting material required to produce pulmonary disease, but not so severe as to destroy the animal before completion of the experiment, had to be worked out.

As will be seen subsequently, 5 weekly feedings were at first given, but, on account of high mortality in these animals, 2 feedings a week apart were later used to produce marked disease of the lung and this dose did not kill too rapidly. This procedure was therefore finally followed in the experiment in which superimposed cutaneous infection was established following ingestion tuberculosis.

From the first, some variations in the ability of guinea pigs to absorb tubercle bacilli from the intestinal tract were noted. In 145 guinea pigs, all but 11 were readily infected. Of this latter group, 6 required 7 feedings to give a positive tuberculin test and, in the other 5, positive results were not obtained even after 8 gastric ingestions. These variations from the average cannot be explained on the ground of increased resistance to the organism, as subsequent cutaneous inoculations showed no change from the average result in the control animal.

Cutaneous disease was produced by injecting into the skin of the abdomen a

suspension of H37 containing .005 mg. of bacilli. This was repeated weekly for five weeks. Where the cutaneous infection was superimposed on animals already fed with tubercle bacilli, the inoculations into the skin were not given until a positive tuberculin test had been obtained.

The cutaneous lesions ulcerated in only 5 instances, drained a local abscess and healed in from three to five weeks. The repeated injections of the skin of the abdomen gradually gave rise to involvement of the axillary and inguinal lymph nodes. Softening occurred in 17 animals. With a survival period of four months or more, fibrosis became more and more marked and few bacilli remained at autopsy.

The excretion of ingested tubercle bacilli in the feces was observed, using the method advocated by Petroff, as described by Willis. From the excreta collected, twenty-four to forty-eight hours after feeding, ground in saturated salt solution and incubated three hours with an equal volume of normal sodium hydroxide, a few acid-fast rods were recovered. Rarely a few clumps were noted but in most specimens the bacilli were scattered and few in number.

Controls: Three groups of controls were used. The first group of 15 animals was given cutaneous infection, and the second and third of 15 and 8 animals, respectively, infection by ingestion.

The routine in producing cutaneous disease consisted of 5 weekly inoculations of the skin of the abdomen, each being made with .005 mg. of tubercle bacilli, the total amount used by weight being .025 mg.

Of the animals so infected, 2 died of intercurrent infection and 2 of extensive tuberculous pneumonia at the end of two months. Three animals lived from four to five months and showed marked involvement of the inguinal and axillary nodes. Extensive disease was found in the lungs and spleen. The liver showed moderate infection in one instance and in 2 others no macroscopic lesions were apparent. The remaining 8 animals of this group lived on an average of seven and a half months following the cutaneous infection. At autopsy pulmonary disease was extensive in 3 animals and moderately wide-spread in 5. The extensive infection of the spleen closely followed that of the lungs, but in the liver none of this group showed as much disease as was found in the other organs and in 2 no visible lesions were apparent.

In the second lot of controls, infection through ingestion was produced as previously described, namely, 5 weekly feedings of .01 mg. virulent bacilli in suspension, to a total by weight of .05 mg.

A positive tuberculin test could not be obtained, even after several attempts, in 5 animals in spite of the mass of bacilli used, and they were discarded. Two died of intercurrent pneumonia. Of the remaining 8, 3 lived from two to three months, and at autopsy showed massive disease of the lungs, but in 2 of these, only a few scattered lesions occurred in liver or spleen. The remaining 5 animals succumbed to the disease after eight months, all of them showing extensive disease of the lungs, liver and spleen. In all these animals fresh preparations were made at autopsy and stained for tubercle bacilli. Numerous masses of tubercle bacilli were uniformly found in preparations from lungs and

spleen. In the liver they were also easily detected except where necrosis was extensive. Sections stained for acid-fast bacilli revealed many bacilli in the lungs and, to a somewhat lesser degree, in the spleen and liver.

In the third control group of 8 animals, 2 gastric feedings were given, totaling .02 mg. of bacilli. Four animals lived from two to four months after infection and all showed pulmonary lesions together with slight involvement of liver and spleen with one exception where the latter was riddled with disease. The remaining 4 animals succumbed in eight to nine months of very extensive disease of the lungs and spleen and moderate involvement of the liver. Fresh preparations made at time of autopsy showed tubercle bacilli to be abundant in all the organs of 7 out of the 8 animals.

In all three of these control groups no marked enlargement of the liver or spleen was found.

CUTANEOUS INFECTION SUPPLEMENTED BY GASTRIC FEEDINGS

Coincident with the group infection of controls, 22 animals were used in which cutaneous infection preceded gastric feeding with tubercle bacilli. The same procedure was repeated both in regard to the production of cutaneous and gastric disease, namely, 5 skin inoculations totaling .025 mg. and 5 gastric feedings to the amount of .05 mg.

In what quantity fed bacilli were absorbed from the intestinal tract is open to question, as we have no certain knowledge as to whether absorption was retarded or expedited by the preëxisting cutaneous disease. The following results, however, have some bearing on the results obtained in subsequent experiments. Two of these animals died within two months following multiple infection. The total average length of life was between six and seven months. In 10 of 12 animals which suvived four months or more, the liver and also the spleen showed very marked enlargement.

In this group the lung was involved to a mild degree in 15 and marked in 7 animals. The extent of the tuberculous involvement of liver and spleen was just the reverse when compared with that in the lung. In sections and in fresh preparations tubercle bacilli were noted more frequently and in much larger numbers in the lung than in the liver.

SUPERIMPOSED CUTANEOUS INFECTIONS

In the first group of 18 animals, 5 consecutive weekly feedings were given, the total dosage of tubercle bacilli being .05 mg. After an interval of two weeks, when a positive tuberculin test was obtained, a series of weekly intracutaneous abdominal injections was begun to the amount of .005 mg. per week. It was the intention to give each animal a total of 5 such inoculations, but disease previously induced by ingestion was so overwhelming that 9 died before the experiment was completed, 6 survived only 5 feedings and one cutaneous injection. At autopsy these animals showed very extensive pulmonary disease and both liver and spleen contained many soft tubercles with considerable variation in size and extent.

The average length of life of those remaining, with 3 exceptions, was between

three and four months and in these the tuberculous lesions varied little from those described above. Two of the 3 exceptions lived four months. In them the liver was greatly enlarged and sections showed a noticeable effort at repair.

One animal survived the heavy double infection and was killed at the end of twelve months. It had generalized involvement of the cervical, inguinal, axillary and tracheobronchial lymph nodes. These were all firm with fibrous tissue. Sections of the liver showed scattered areas between lobules of dense fibrous tissue with no typical tubercles. The lung also showed areas of fibrosis, but no giant cells. Only in the spleen were typical tubercles found, partly organized and containing tubercle bacilli. No bacilli could be found either in fresh preparations or in sections of lung or liver.

In a second series of 53 guinea pigs, receiving 2 gastric feedings a week apart of .01 mg. of tubercle bacilli per week, in which a positive tuberculin test was obtained, cutaneous infection was produced as previously described. As the number of feedings was limited to 2, the burden of the disease from this source was not as heavy as that in the first group, and with a longer survival period the opportunity for study of interreaction of pulmonary and cutaneous infection was possible. Ten animals died before the experiment was completed. Twenty succumbed to the disease in from one to three months following superimposed infection. In these, the lungs showed wide-spread disease with very little if any formation of fibrous tissue in and about the tuberculous lesions. Enlargement of the liver began to be noticeable at about the third month, but up to this time the number of lesions in the spleen and liver was small. Twenty-three animals lived from three to six months. In 14 of these, sections of lung showed striking evidence of repair with fibrous tissue appearing in and about the pulmonary lesions. Almost without exception there was very marked enlargement of the liver, and in 6 animals the spleen attained enormous size. The extent of tubercle formation in both these organs was marked, quite in contrast to those that lived only three months. A generalized fibrosis of many of the lymph nodes was noteworthy.

Eight animals lived from six to eight months. In all of these, macroscopic pulmonary lesions were few and many were dense and circumscribed. The liver and spleen were, with only one exception, greatly enlarged. The liver contained a few areas of necrosis and infection, but in the spleen these were still quite apparent. Hematoxylin and eosin stained sections from this group of animals that lived the longest showed a great amount of repair with fibrous tissue. In many fresh preparations no tubercle bacilli could be demonstrated in 8 of the animals surviving from four to eight months. The implication here is that, with a longer period of survival, the organ might well have entirely cleared itself of the infection.

One animal in this group of superimposed infections was sacrificed at the end of twelve months. It had received 4 gastric feedings and 5 intracutaneous injections. Sections of the liver showed no definite tubercles, but there were still a few areas of cellular infiltration in both spleen and lungs. In fresh preparations, tubercle bacilli could only be obtained from the inguinal nodes and lung.

In Soper's work with the bovine organism in rabbits, the interrelationship of liver reaction to infection and repair of pulmonary disease was noted. This has been equally true in guinea pigs in superimposed infection with the human bacillus.

DISCUSSION

Superimposed cutaneous tuberculosis in the guinea pig with pulmonary tuberculosis has a distinctly modifying effect on the disease in the lung through the response of the liver to infection. Great enlargement, destruction of the bacillus and tissue repair have steadily progressed in the liver at the same period in the disease as improvement has been noticeable in the lung. It would appear that twice, even in massive tuberculous infection, has arrest of the disease been brought about by the stimulation of the liver by superimposed infection.

SUMMARY

Ingestion tuberculosis by the method of Calmette gives rise to disseminated pulmonary disease in guinea pigs.

The response of the liver to superimposed cutaneous disease and its favorable effect on pulmonary tuberculosis are described.

SUMARIO

La tuberculosis de ingestión producida por la técnica de Calmette, provoca afección pulmonar difusa en el cobayo.

Descríbense aquí la respuesta del hígado a la afección cutánea sobrepuesta y su efecto favorable sobre la tuberculosis pulmonar.

REFERENCES

(1) Koch, R.: The Aetiology of Tuberculosis, translation by Pinner and Pinner, Nat. Tuberc. A., New York, 1932.
(2) Trudeau, E. L.: Tr. A. Am. Physicians, 1903, p. 18.
(3) Nichols, J. L.: Med. News New York, 1905, *87*, 638.
(4) Schwabacher, H., and Wilson, G. S.: J. Path. & Bact., 1938, *46*, 535.
(5) Krause, A. K., and Willis, H. S.: Am. Rev. Tuberc., 1926, *14*, 316.
(6) Willis, H. S.: Am. Rev. Tuberc., 1925, *11*, 427.
(7) Lurie, M. B.: J. Exper. Med., 1939, *69*, 579.
(8) Lurie, M. B.: J. Exper. Med., 1939, *69*, 555.
(9) Soper, W. B.: Am. Rev. Tuberc., 1917, *1*, 385.
(10) Kutschera-Aichbergen: Wien. klin. Wchnschr., 1937, *50*, 1542.
(11) Tufts, L.: J. Immunol., 1936, *21*, 85.
(12) Michelson, H. E.: Journal-Lancet, 1942, *62*, 250.
(13) Calmette, A.: Tubercle Bacillus Infection, and Tuberculosis in Man and Animals, translation by Soper and Smith, Williams & Wilkins, Baltimore, 1923.
(14) Willis, H. S.: Laboratory Diagnosis and Experimental Methods in Tuberculosis, Charles C Thomas, Baltimore, 1928.
(15) Gerstl, B., Tennant, R., and Pelzman, O.: Yale J. Biol. & Med., 1945, *17*, 455.

THE SULPHONES IN CLINICAL TUBERCULOSIS[1,2]

FREDERICK TICE, HENRY C. SWEANY AND RICHARD DAVISON

INTRODUCTION

The following report is a condensed analysis of the therapeutic studies in far advanced pulmonary tuberculosis of two sulphone compounds, "diasone"[3] and "1048."[4] Preliminary studies (1, 2) of the effects of these and other sulphones in animals have been published.

Feldman and coworkers, of the Mayo Clinic (3 to 7), were the first to investigate the effects of promin in animals. Medlar and Sasano (8), Smith, Emmart and Westfall (9), Steenken, Heise and Wolinsky (10), Steinbach and Duca (11), Barach, Molomut and Soroka (12), and Tytler (13) continued the studies. Other sulphones, including diasone, and other related compounds were also studied in animals by Callomon (14). Feldman and associates (15) investigated promizole and found it to be less toxic than promin. The parent substance, diaminodiphenylsulphone, was also studied by Feldman (16), but he obtained less favorable results than with other sulphones. With few exceptions reports show striking results in the inhibition of the growth of tubercle bacilli either in cultures or in animals or in both. All this work has been reviewed recently by Tytler (17).

In the field of human tuberculosis, Hinshaw, Pfuetze and Feldman (18) treated 106 patients with promin. They observed an improvement in a fair percentage of the patients and no improvement in about an equal number. They also noted cyanosis and other toxemic symptoms that required close watching. Petter and Prenzlau (19) found that diasone exerted a favorable influence on patients with moderately advanced and early far advanced tuberculosis, although they too encountered many aggravating toxemic effects. Faget and associates (20) used promin in leprous patients with some favorable results together with many toxemic manifestations. Heaf and associates (21) found some improvement in promin-treated tuberculous patients, whereas Willis (22) was doubtful of any improvement in a group of 23 treated cases. Thus, in human tuberculosis, the preliminary results with sulphones have not fulfilled the hopes engendered by the animal experiments.

In the majority of treated patients, irrespective of the mode of administration, cyanosis was found to result from a hemolytic anemia. The problem has been studied extensively

[1] From the Clinical and Research Laboratories of the City of Chicago Municipal Tuberculosis Sanitarium.

[2] The present study has involved the efforts of practically the entire medical, nursing and laboratory personnel of the Institution. Special acknowledgments should be given to Dr. Karl Henrichsen for valuable aid in the clinical work; Dr. Rosalind Klaas for the blood chemistry studies; Dr. Ben C. Sher for the control analyses of the drug in blood and urine; to Miss Wilma Cannemeyer for the blood cytology studies and to Messrs. Don Warriner and Frank Giermak for the many calculations.

[3] "Diasone" is disodium-formaldehyde-sulphoxylate-diaminodiphenylsulphone and was furnished through the courtesy of Abbott Laboratories of North Chicago, Illinois, by Dr. George R. Hazel.

[4] The "1048" was originally prepared by Dr. M. S. Kharasch at the University of Chicago. It is 4-4′-diaminodiphenylsulphone N-N′ cystine sodium sulphonate and was furnished through the courtesy of Eli Lilly and Company of Indianapolis, Indiana, by Dr. H. A. Shonle.

in guinea pigs by Callomon (14), Higgins (23) and Corper and Cohn (24). The latter authors ascribe the beneficial effects of the sulphones largely to the anoxia resulting from the anemia produced. Practically all workers have observed the phenomenon, but there is general agreement that most patients soon overcome the anoxia if the dosage is properly regulated. Except with small doses there are other serious toxemic effects, such as nausea, headache, rise in temperature, increased cough and nervousness.

Near the outset, therefore, it became necessary to disregard most of the methods and standards worked out in guinea pig experiments and to seek new data for the administration of the drug in human beings. Hinshaw, Feldman and Pfuetze (28) estimated the tolerance of patients for promin to be one-twentieth to one-fortieth of that of the guinea pig. They found that they could give no more than 1.2 to 1.6 g. a day with safety. A similar dosage was found useful by Dancy, Schmidt and Wilkie (25), provided occasional rest periods of five to seven days were given. Faget and associates (20) observed that 0.5 to 1.0 g. by mouth were not tolerated long in leprous patients, and so they tried the intravenous method by which they gave, with certain interruptions, as much as 5 g. daily without ill effects. Although the patients were able to tolerate many times the maximum oral dosage, yet there was difficulty in the maintenance of a sufficiently high concentration in the blood. Johnson (26), while giving up to 15 g. a day, found that 95 per cent was excreted in the urine.

In order to produce a higher concentration, Zucker, Pinner and Hyman (27) introduced the continuous *intravenous drip* method of administration. After a single 5 g. injection of promin they found that the blood levels ranged from 5.0 to 21.6 mg. per cent after fifteen to thirty minutes, then fell rapidly to 2.8 to 4.0 per cent after two hours, and to traces after twenty-four hours. By continuous injection they were able to raise the blood level during the day from a low of 1.3 mg. per cent to a high of 15.4 mg. per cent, with the average around 10 mg. per cent. The level fell again during the night's rest to a minimum of around 2.0 mg. per cent. By this method they were able to maintain a high concentration of the drug for ten hours a day, six days a week, during periods of four to seven months. They noted some toxemic effects, but these were not very serious. However, there was no improvement of the disease process, although they were able to give as much as 25 g. a day.

Since none of the intravenously treated patients seemed to fare any better than those treated by oral administration, and since the latter method possesses some advantages, the recent tendency has been to adopt this method. The blood concentration apparently increases more slowly, reaches a lower level, but remains longer at its maximum than in the case of the intravenous method. There is also the possibility suggested by Hinshaw, Feldman and Pfuetze (28) that a conjugate may be produced in the gastrointestinal tract which may have a beneficial therapeutic effect.

Irrespective of any theoretical beneficial effects resulting from oral administration, sulphones given by that method are definitely more toxic than when given intravenously. The increased toxicity of the oral route is ascribed partly to diaminodiphenylsulphone which is easily split from the molecule. Conjugates of unknown character are found. Johnson (26) reports that 20 per cent of the drug recovered in the urine is conjugated. All toxicity, however, cannot be explained on this basis since anemia develops following every mode of administration.

In spite of the negative effect on the disease when the drug is given intravenously and the necessity of low dosage for human beings by the oral method, a feeling of optimism has prevailed with regard to the possibilities of sulphones in tuberculosis. There has been a hope that an "intermediate conjugate" or other possible derivative may produce

a better effect than the pure drug. Up to the present time, however, none of the hopes have been definitely realized, favorable articles in the lay press notwithstanding.

After an analysis of the reports on the treatment of human tuberculosis with sulphone compounds, a familiar pattern of results is observed. Some of the early and perhaps "good reacting" cases appear to improve; a larger number manifest a slightly favorable or indifferent result; and certain severe types, like tuberculous meningitis, are not favorably affected in the least. In general, the course of the patients as a whole is similar to that of any group of tuberculous patients on routine treatment with the exception that the evolution of the disease process in a few cases may have been accelerated in one direction or the other.

With these facts confronting us, a properly controlled study seemed not only expedient but mandatory. The mere addition of another uncontrolled experiment to the rapidly accumulating literature would contribute nothing of value and only further confuse the issue. It may be contended that any therapeutic result not evident by ordinary means of observation will not be worthy of consideration anyway, but the literature contains numerous reports on remedies which have been hailed as cures as a result of objective and subjective studies, but which have later failed to measure up to the expectations created by the earlier claims. If a drug ever appears that will cause every ill tuberculous patient to recover within four to six months' time, or will cure tuberculous meningitis, controls will not be needed; but it is doubtful that such a drug will ever be found. When it is realized that, according to Braeuning (29), over 30 per cent of frank tuberculosis heals spontaneously, any uncontrolled results become of limited value. In the absence of a "heroic cure," therefore, we must attempt accurately to evaluate *slight* or *moderate improvement, no improvement*, or what is of greater importance, to determine *whether there is actually injury produced by the new therapy.*

Controlled experiments in the treatment of tuberculosis are not new. There were several precedents listed by Sweany in the discussion of Hinshaw and Feldman's (30) reports. The gradual evolution of the matched control method is an outgrowth of the attempt to evaluate specific therapy in tuberculosis—one of the most variable of all diseases. The method used here is that developed by Sweany, Clancy, Radford and Hunter (31) in their studies on the therapeutic effect of vitamin C on tuberculosis. These authors used for the first time a numerical "handicapping" system, with merits and demerits, in the matching of treated patients and their controls. This procedure is deemed a check on the classical method of study because appearances in tuberculosis are often deceiving. A review of some of the variable factors will show the need for a means of close matching in a therapeutic experiment in human tuberculosis.

As in few other diseases, the future course of the tuberculous process cannot always be foretold. The critical pathological changes, for example, may be unnoticed or they may be detected only long after they have taken place.

Every tuberculous infection begins as an inflammation chiefly in the form of "tubercle" even though it may be microscopic; the primary infection conforms to the "law" of "similar adenopathies," following along the adjacent lymphatics and finally reaching the bloodstream. Living virulent tubercle bacilli may be obtained from the lesions during the first year or two of the infection, and the cells of the body become sensitized to the infection as shown by the tuberculin reaction. No doubt there are also minor changes in the percentage and type of blood cells and in the colloid stability of the blood serum. Perhaps 95 per cent or more of all tuberculous infections do not reveal manifestations beyond those mentioned above, and heal uneventfully. The possibility of these small lesions spreading to extensive disease, however, is always present as long as they contain

living bacilli, and a small percentage do develop into active disease. The size of the lesion is not so important as the number and virulence of the bacilli, resistance of the host, and accidental circumstances occurring at a critical period during the encapsulation of the tubercle. The methods of exacerbation into disease are various and each type may result in a different course. Some lesions spread gradually, some rapidly by direct extension, some slowly or rapidly by the bronchi or by the blood or lymph vascular routes. In some cases a reinfection develops into disease in a variety of ways.

In the evolution of the disease, symptoms do not always parallel the pathological changes. Sometimes the disease may be relatively benign even with advanced lesions. Usually the disease is first discovered on a roentgenogram, although suspicion may be aroused by minor episodes of fever, pleurisy or hemorrhage. Occasionally the exacerbation of the smaller lesions to larger ones results in severe clinical symptoms with fever and physical findings of exudation. The patients who are overwhelmed by the first infection are relatively few in number and usually have a poor prognosis because of the large dosage or high virulence of the bacilli. Some patients develop generalized disease with a "typhoid syndrome" or with terminal meningitis. Others develop extrapulmonary disease with a wide range of symptoms. Until the extrapulmonary foci reach an advanced stage it is not always possible to detect the influence they exert on the patient. Finally, in all progressive cases there comes a time, different for every case, when many and severe clinical symptoms appear.

During the long and gradual crescendo of progressive changes there may be unpredictable reversals of the process with all degrees of healing. Healing and progression may take place alternately or simultaneously.

In addition to the differences noted above, all the changes may be modified by race, age and sex of the host. There are also inherent individual differences based on physical type and affected by dietary deficiencies and endocrine unbalance. Some of these factors have been clearly shown to influence the course of tuberculosis in different families of rabbits by Lurie (32) and there does not seem to be any valid reason why they may not play a rôle in human tuberculosis.

The course and outcome of tuberculosis is furthermore dependent upon the quality of the lesion, especially the relative degrees of fibrosis and exudation. Accordingly, the results of treatment must be evaluated as much as possible in qualitative terms. A recent infiltrative process cannot be compared with an old fibroid type of lesion because the old fibroid tissue represents former healing. The clearing of infiltrative lesions, the forming of new fibrous tissue with the shrinking of parenchymal lesions and cavities, and deposition of calcium are the only true clinical indicators of healing.

As nearly as possible comparable lesions should be present in both the treated and control cases. Most of these factors are best evaluated by roentgenological methods, although clinical methods based on clinical experience will always be a guiding compass which must never be disregarded.

After a proper evaluation of the accessible variables of the disease and the clinical methods of control, much uncertainty still remains which may be detected only, if at all, by laboratory methods. Most of the intrinsic changes in the disease are best reflected quantitatively in the cytological, chemical and physiochemical constituents of the blood. In fact, laboratory tests are the best means of evaluating the patient's condition in a quantitative manner.

It is clear, therefore, that patients must be selected for teatment who are understood biologically, who have enough demonstrable disease to be observed either by clinical, roentgenological or laboratory methods, but who are not hopeless, and whose disease

process is known approximately with respect to its duration in the body and its qualitative features.

Under the best of circumstances, however, cases that are matched closely may diverge gradually or abruptly because of the many differences of the lesions listed above. A patient may proceed to a rapid termination or heal eventually without any demonstrable reason. In a large series of cases, however, there is usually a balancing of such irregularities, especially if the cases have been observed for a time before the treatment is begun.

METHODS

After a consideration of the many uncertainties of the disease, it becomes no mean task to formulate a check method by which the disease components may be measured in any particular patient. In the attempt to realize this objective, careful clinical and roentgenological evaluation was given to each case. In addition, the arbitrary numerical system of merits and demerits referred to above (33) was adopted and improved. According to this method the "normal" individual has a zero rating. Deductions are made for race, certain age periods, constitutional factors and sex differences known by long observation and experience to cause a variation in the course of an acquired tuberculosis. Deductions are also made for roentgenological and clinical variations from the normal. In like manner, abnormal chemical and cytological changes in the blood and certain complications reduce the patient's prognosis and are added to the total handicap.

It must be emphasized that this numerical method is purely arbitrary and makes no pretense at face-value accuracy. There is also no way to allow for dosage and virulence of the bacilli, except to observe the patients for a time before treatment. When applied to all cases alike by the same individuals, however, the method gives a closer approximation to the true evaluation of the patient's condition than can be obtained by mere qualitative observations.

The principal requirement in applying such a handicap method is that the same system be maintained throughout and the same group of people apply the method in any given experiment. In this way the personal element which is prone to change from time to time will largely be controlled and the quantity and quality of the disease as well as the type of the host will be more closely approximated.

There were nineteen different factors selected and evaluated for the experiment.[5] Five of these are fixed for a given individual and do not vary with the course of the disease. These five include age, sex, race, habitat and constitution. Of the variable factors two were calculated from roentgenological data, four from clinical observations and eight from the results of laboratory tests.

The algebraic sum of all the factors forms a "handicap value" which has been called a "prognosis quotient" and designated in table 3 as P. Q.

After the prognosis quotient was found for each patient included in the study, the process of matching was carried out. Patients within the same age period,

[5] The details of the handicapping method, which are rather extensive, may be obtained by communicating with the authors.

of the same sex, and as far as possible of the same race and constitution were grouped together. The quality and quantity of the lesions and clinical findings were also matched within a reasonable degree of accuracy. Finally, the total prognosis quotient was matched within 25 per cent—most within 10 per cent.

The record cards of the pairs of matched cases were separated into two piles on an alphabetical basis. Patients having the higher letter of the alphabet, beginning with the surname, were placed in one pile and the others in another pile. A coin was flipped to determine which group should be treated. The remaining group served as the control. At the beginning of the matching most of the factors could be matched rather closely. As the pairs of cases were gradually removed by matching, there was left a more dissimilar residue. The treated patient's type and condition became more unlike the control and consequently the matching became less accurate.

In the experiments to be reported, the Institution was canvassed for several weeks in order to obtain the cases best suited for the study. Patients for whom collapse therapy was not deemed advisable were generally selected. Most of the cases were seriously ill, but none was critically ill when selected. In fact, the majority of the patients was considered to have a fair to good chance of recovery. Cases with disturbing complications were rejected unless controls with the same complications were available. Practically every patient had some recent infiltrative lesions which could be observed by roentgenological study.

All the patients were treated as nearly alike as possible as to diet and general management, no special or accessory treatment was given any of the patients while on the experiment, except in emergency, and the control patient C-7-A, who had surgical treatment.

Each control patient received placebo capsules under the guise of the new drug.

The patients were visited daily by their regular physicians. One of the authors (S) visited each patient once a week to check on the various details of the treatment, to observe the objective appearances of the patient and to obtain a subjective account of his or her condition.

The amount of each drug (diasone and "1048") was given according to the patient's tolerance. The initial dosage was based on the recommendations of Feldman and Pfuetze (18) for promin and Petter and Prenzlau (19) for diasone, and modified according to each patient's tolerance. Patients manifesting nausea, nervousness and cyanosis were carefully watched. As pointed out by the above mentioned authors, there was a definite although variable degree of cyanosis in practically every case, but most patients gradually acquired a tolerance and adjusted themselves to the loss of hemoglobin and to the resulting anoxia. The nausea and nervous reactions, however, were of a more serious nature. Few patients who manifested these reactions were ever able to continue the treatment long without a reduction in dosage. Some had to be taken off the drug entirely.

Chemical analyses for the drug in both blood and urine were used to follow the treatment. It was very necessary to see whether the patients were taking the drug and if they were taking it to see whether it was being absorbed. The

chemical analyses were also good checks on possible errors and deliberate "trading" of capsules. All in all, very few irregularities were discovered.

The sputum was examined for tubercle bacilli at regular monthly intervals and, in most cases, the amount of the sputum was recorded. Cultures were made on a selected group of treated cases. Complete physical examinations were performed at the end of the experiments as at the beginning and a follow-up was made six months after the experiment was ended. Roentgenograms were taken before and at the end of the treatment. Treatment was continued for approximately four months unless poor tolerance of the drug or the condition of the patients otherwise forbade further drug treatment.

EXPERIMENTAL PART

From a group of 200 patients considered, 160 were selected for preliminary study and 108 of the latter were chosen for treatment with one or the other of the drugs. The 108 patients were divided into two groups, 60 for the "diasone" study and 48 for the "1048." Of these two groups, however, only 32 of the former and 16 of the latter (a total of 48) were carried uninterruptedly to the end. Many pairs were broken by unexpected accidents or death; many developed or were found to have disturbing complications, and in several the matching was found not to be sufficiently accurate.

To cite one example of error, one treated patient who revealed a definite improvement with diasone was found to have an upper lobe abscess and not tuberculosis. The case was submitted by the floor doctor as tuberculous, but was ultimately discovered to have an abscess. Later a lobectomy was performed by one of us (D) and the patient made a complete recovery. This case with its control is subtracted from the original 108, leaving 106 actually tuberculous. The same treated case is mentioned later as developing diabetes during diasone therapy.

DISCUSSION

In table 1 various significant symptoms are recorded to show the percentage increase or decrease after the beginning of the experiment. The decrease in

TABLE 1

Increase of important symptoms of cases treated with diasone and 24 treated with "1048" together with their controls

(Expressed in percentage of the respective totals)

DRUG	TEMPERATURE		PULSE		COUGH		WEAKNESS		NAUSEA		HEMORRHAGE		CYANOSIS		DYSPNEA	
	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C
Diasone........	41.4	20.6	20.7	3.4	3.4	31.0	13.8	10.3	20.7	6.9	13.8	3.4	48.3	3.4	17.2	0
"1048".........	20.8	25.0	29.2	4.2	20.8	20.8	25.0	8.3	20.8	16.6	4.2	8.3	66.7	0	16.6	12.5

T = Treated cases.
C = Controls.

symptoms is no more than one would expect in any group of far advanced sanitarium patients and is about equal in the treated and control cases. Certain conditions were produced, however, by the drugs, most important of which was the cyanosis observed by others and really of much less consequence than appearances would seem to warrant. The temperature and especially pulse were increased more in the treated than in the controls. Cough seemed to be less frequent in diasone-treated cases. The sputum quantity remained about the same in all cases.

An analysis of the symptoms of pain is interesting. After eliminating the cases with peptic ulcers, pain was about equally distributed between treated and control patients One patient treated with "1048" had a generalized grip-like pain in joints and muscles. Pain referred to the stomach included 2 patients treated with diasone, one treated with "1048" and 2 controls. Abdominal pain was present in one patient treated with diasone and one control. Pain in the chest was present in 2 patients treated with diasone and one treated with "1048;" but there were 3 controls with similar pains. Pain in the kidney region was present in one diasone-treated case with similar symptoms in one control. Pain in the shoulder was present in one control.

TABLE 2

Condition of 58 cases in the diasone experiment six months after the end of the treatment

IMPROVED		UNIMPROVED		DIED		TOTAL
Treated	Controls	Treated	Controls	Treated	Controls	
5	4	14	11	10	14	58

Perspiration, insomnia, hoarseness, chills, blood in stools, nocturia, polyuria, dizziness, skin irritability, headaches, tympanites and diarrhea when present were about equal in treated and control cases.

In the more detailed analyses the findings were divided into the diasone-treated cases and those treated with "1048."

The diasone group: The clinical results of the diasone-treated patients, consisting of 29 treated and 29 control cases, are shown in table 2.

The results are given as found six months after the end of the treatment which was practically a duplication of the immediate results. There was little to choose between the treated and control cases.

In analyzing the complete results, the groups were further divided into well matched cases and cases not well matched. There were 16 of the former and 13 of the latter with their respective controls.

The total diasone given to 30 patients (including one lung abscess) was 3,418 g. for a total of 3,811 patient days. The average amount of diasone administered, therefore, was 0.9 g. per patient per day.

The blood level of diasone was roughly 1 mg. per cent when one g. daily was given, and the amount recovered in the twenty-four hour urine was usually between a third and a half of the intake.

TABLE 3

Complete results of 4 cases treated with sulphones, with a control for each

CASES	TREATMENT				SPUTUM		DRUG LEVELS		
Treatment No	No of Days	Total Gr. of Drug	Dosage Gr Daily	Tolerance	Concentration, tubercle bacilli per field	Quantity, Gr	Date	Blood, mg %	Urine, mg 24 hr (or single spec "S")
D-4	133	177	1.3 1.3	Good	20 20	30 40	3/22 6/13	0.9 1.1	460 129
D-4-A					6 5	30 20			
D-16	113	75	0.7 0.7	Good	1 20	25 0	3/9 4/28 5/26	0.72 0.51 0.81	21 "S" 298
D-16-A.					Neg. Neg	0 0			
C-4	122	61	1.0 0.3	Poor	Neg Neg	40	3/23 4/26 6/15	0.8 1.04 1.5	322
C-4-A					Neg Neg.	25 35			
C-7	108	108	1.0 1.0	Fair	20 p s 20 p s	20 20	3/22 4/26 6/13	3.9 1.5 1.5	880 176
C-7-A .					Neg —	70 —			

Treatment No	LABORATORY								RESULTS						
	Date	Hemoglobin (Dare)	Red Blood Cells (in millions)	White Blood Cells (in thousands)	Polymorphs, %	"Stab" Forms	Segmented	Poly/Lymph Ratio	Lymph/Mono Ratio	Sedimentation Rate	Fibrin	Albumin	Globulin	A/G Ratio	P Q
D-4	1/6 5/15	72 60	4.41 3.92	6.1 10.2	75 73	8 10	63 60	4.4 3.7	1.8 2.4	15 23	1/7 0.54 6/13 0.68	3.41 3.80	3.43 2.83	1.00 1.34	244 323
D-4-A	1/12 5/18	72 65	4.15 4.38	7.6 10.5	65 66	10 7	52 58	2.6 2.5	2.2 3.2	18 25	1/20 0.64 6/8 0.60	3.56 3.34	3.08 2.74	1.10 1.22	249 281
D-16	1/21 5/26	55 60	4.07 4.00	10.7 14.3	81 71	15 13	64 57	5.3 3.4	3.8 2.6	25 23	1/24 0.71 5/26 0.73	3.20 4.0	3.74 3.43	0.86 1.18	384 355
D-16-A.	1/22 5/26	61 62	3.91 4.08	9.2 10.2	77 67	13 9	60 57	4.9 2.6	1.8 3.1	11 12	1/25 0.43 5/31 0.47	3.96 4.45	3.73 3.54	1.06 1.26	253 217
C-4	1/6 5/15	61 70	4.65 3.50	8.3 7.9	71 67	18 10	52 55	4.7 2.7	1.1 2.7	13 8	1/10 0.51 6/15 0.48	3.42 4.10	3.42 2.42	1.00 1.69	239 164
C-4-A	1/12 5/18	77 55	4.47 4.56	6.0 5.1	58 68	6 8	47 50	1.4 2.8	7.4 3.0	17 14	1/18 0.46 6/12 0.30	4.09 4.48	3.02 2.07	1.35 2.16	186 123
C-7	1/6 5/15	68 65	4.71 4.20	7.0 8.0	70 69	7 10	62 57	3.6 2.8	1.7 3.4	15 6	1/10 0.54 6/13 0.42	3.76 4.57	3.79 2.67	1.00 1.71	227 158
C-7-A .	1/12 7/12	70 75	4.19 5.75	8.0 5.2	77 67	7 2	70 65	5.1 2.6	1.9 5.2	4 2	1/20 0.37 7/12 0.36	4.42 4.53	2.53 2.03	1.73 2.23	266 106

Treatment No	CLINICAL RESULTS		X RAY RESULTS AT END OF EXPERIMENT		FIXED P. Q. (AGE, RACE, ETC.)	TOTAL P. Q., TREATED CASES	GAIN OR LOSS, TREATED CASES	TOTAL P. Q. OF CONTROLS	GAIN OR LOSS OF CONTROLS	GAIN OR LOSS OF CASES TREATED OVER CONTROLS	CONDITION SIX MONTHS AFTER
		P Q	General impression at end of experiment	P Q							
D-4	Cough improved, hemorrhage near end of experiment, weight same	0 20	Slight disease regression	130 130	35	409 508	−99			+48	Unimproved, slight progressive case
D-4-A	Appetite improved, increased cough, 30% loss of weight	70 120	Slight disease progression	110 175	35			464 611	−147		Died 12/9/44
D-16	Cough decreased, slight cyanosis, temperature 100°F, condition unchanged	60 35	Essentially stationary	160 160	100	701 650	+51			−27	Stationary or slight clearing, fair condition
D-16-A.	Improved, slight loss of appetite, gain in weight	45 0	Essentially stationary	200 200	75			573 492	+81		Stationary
C-4	Cough decreased, appetite improved, but cyanotic, condition unchanged	+5 0	Essentially Stationary	70 70	0	304 234	+70			−3	Stationary
C-4-A	No complaints, decreased sputum, condition unchanged	0 0	Slight improvement	50 40	60			296 223	+73		Stationary
C-7	Slight nausea, gas pains, streaking of sputum, condition unchanged	10 15	Moderate disease progression	110 130	50	397 353	+44			−116	Stationary
C-7-A .	Condition improved	+10 +10	Stationary	110 110	20			3[illegible]6 22[illegible]	+1[illegible]0		Thoracoplasty, improved

D = Diasone. C = "1048". A = Placebo.
The figures with virgule between give the date in 1944.
N[illegible] [illegible] not determined

Albumin of 0.1 per cent or more was found more frequently in the treated cases than in the controls, although only 2 or 3 seemed to develop kidney damage as a direct result of the drugs. Cultures were made of the sputum of a representative number of treated cases and no bactericidal effect could be detected.

Plates 1 and 2 show the roentgenological pictures of 4 cases, 2 treated and 2 controls, before and after the experiment.

In table 3 the complete analysis of 4 cases and 4 controls is given. The first 4 cases include 2 cases treated with diasone and their respective controls. They represent the best results obtained with diasone. The histories will be given briefly together with brief roentgenographic interpretation.

Case Reports

D-4 (R. F.) was a 58 year old street-car conductor of Dutch ancestry. His complete record is tabulated as the first case in table 3. The patient tolerated very well 177 g. in 133 days. Near the end of the experiment the patient developed an elevation of temperature and repeated small hemorrhages. He was put on "A" capsule (placebo) after June 15, 1944. The roentgenological findings were as follows: Before treatment (1/11/44) there was a marked fibroid lesion present in the whole right upper lung lobe containing contracted heavy-walled cavities. Discrete fibrocaseous, acinous-nodose lesions were scattered in the middle third of the lung. Early cavity formation was present in the left apex. There was also a slightly clearing acinous-nodose tuberculosis throughout the upper two-thirds of the lung (plate 1, figure 1a). After treatment (5/10/44) there was a very slight disease progression (plate 1, figure 1b). The patient was unimproved at the end of the experiment. The 409, or total number of demerits, is what has been designated as the "prognosis quotient" or P. Q. The demerits changed from 409 to 508, a loss of 99 points, which suggests a deterioration of the patient's condition.

The control of the preceding case, *D-4-A* (J. R.), was a 57 year old American male of German-French ancestry. His clinical condition deteriorated, a fact revealed also by the following roentgenological description. Before the beginning of the study (1/10/44) the roentgenogram revealed a fibroulcerative tuberculosis in the upper half of the right lung with a 5 x 7 cm. cavity in the upper lobe and a 7 cm. cavity in the apex of the lower lobe. More acute ulcerative tuberculosis was present in the left mid-field. Two cavities were present measuring 3 to 4 cm. (plate 1, figure 2a). At the end of the treatment (5/10/44) there was a noticeable progression with enlargement of all cavities and extension of acinous-nodose tuberculous lesions (plate 1, figure 2b). At the beginning of

---

PLATE 1

FIG. 1a (upper left). Roentgenogram, taken on January 11, 1944, of patient R. F. (D-4) treated with 177 grams of diasone in 137 days.

FIG. 1b (upper right). The same case on May 10, 1944. There is possibly a slight clearing noted.

FIG. 2a (lower left). Roentgenogram, taken on January 10, 1944, of patient J. R. (D-4-A).

FIG. 2b (lower right). Same case on May 10, 1944. There is possibly a slight disease progression.

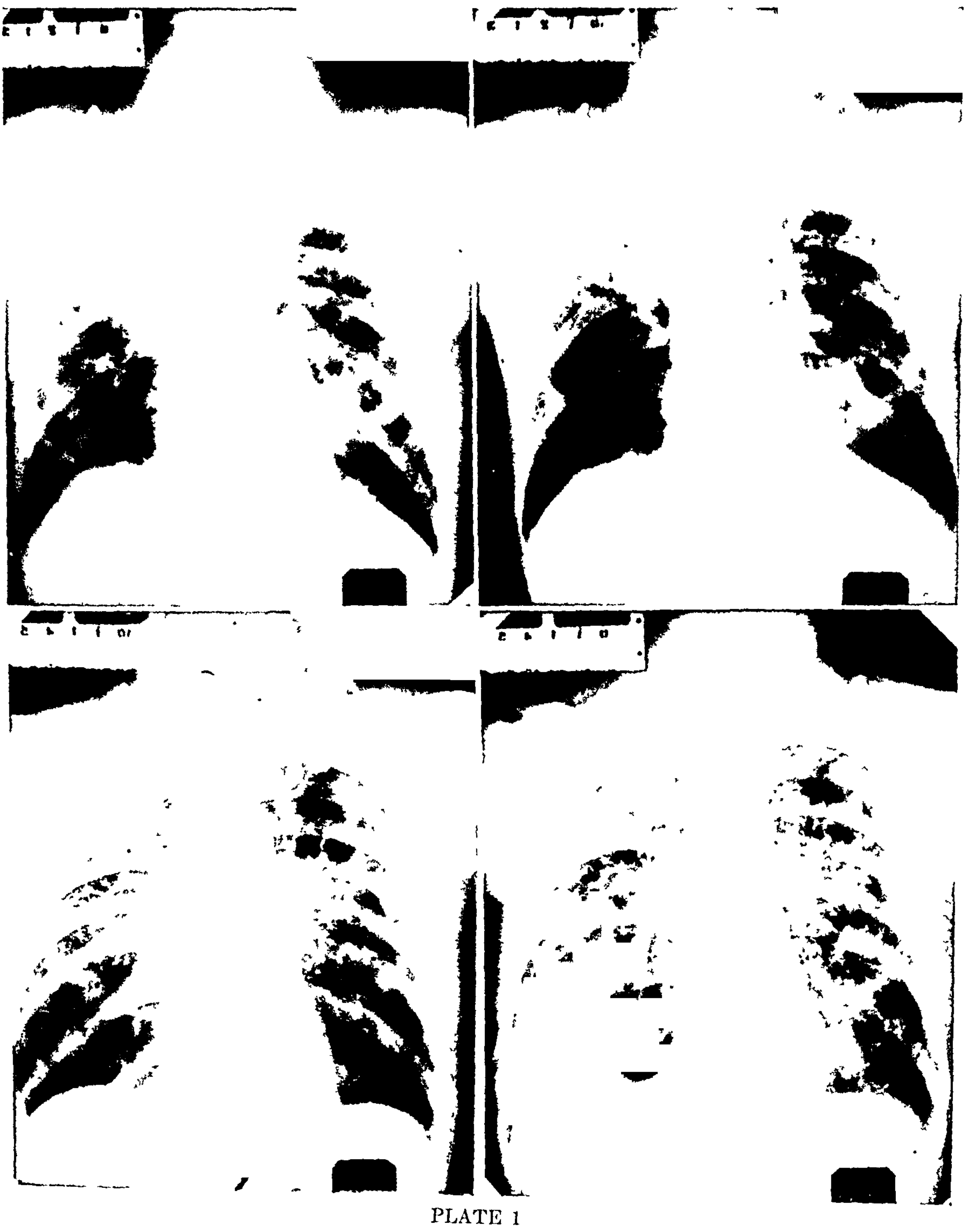


PLATE 1

the treatment the P. Q. was 464 (12 per cent more than the treated case). At the end of the experiment the P. Q. was 611, a loss of 147 points, showing about equally in all the determining factors. Since the loss of the treated case was only 99, the net gain of the treated case over the control was 48 points.

Six months after the end of the experiment the treated case was unimproved, while the control was a terminal case, dying on December 9, 1944, eleven months after the beginning of the experiment.

D-16 (D. L.) was an 18 year old female of Polish descent (table 3). She received 75 g. of diasone in 113 days and, except for a slight cyanosis, she experienced no ill effects of the drug. Towards the end she claimed she felt "much better." Her P. Q. went from 700 to 650, a gain of 50 points. Note the slight clearing of the roentgenogram (plate 2, figures 1a and 1b). The roentgenological description was a follows: On January 12, 1944 there was a soft infiltrative tuberculosis in the whole right lung and organized pleural effusion with a faint diffuse infiltrate in the base of the left lung. On June 5, 1944 there was a slight clearing of the infiltrate in the left base but no great change otherwise. Six months later the process was stationary.

The control, *D-16-A* (M. T.), was a 20 year old American girl of French ancestry (table 3) who thought she "rested better at night" for a while, and then she developed an indifference, saying she felt "O. K." or "no change" on every visit. Her P. Q. went from 573 to 492, a gain of 81 points. Six months later her condition was stationary. Although the control showed a few points over the treated case there was really little difference between the 2 patients. A description of the roentgenograms follows: On January 12, 1944 there was a consolidation and partial atelectasis and consolidation of the right lung. A small cavity was present in the left upper lobe, measuring 2 cm., with clearing acinous-nodose tubercles down to the second rib. On May 4, 1944 there was practically no change; if anything a slight clearing could be noted (plate 2, figures 2a and 2b).

The total demerit points for the diasone-treated cases were 8,470 before treatment and 8,740 after treatment, a slight loss. The control cases totaled 8,200 points before and after the treatment. No favorable change, therefore, can be ascribed to the treatment in the treated group by any method of reckoning. In fact, as a group they fared slightly worse than the controls. The figures, however, are well within the limits of experimental error.

One pair of cases referred to before was eliminated because of a mistaken diagnosis, but the treated patient developed diabetes during the treatment.

The "1048" group: The "1048" compound, which was found to be effective in

---

PLATE 2

FIG. 1a (upper left). Roentgenogram, taken on January 12, 1944, of D. L. (D-16) who received 75 grams of diasone in 113 days.

FIG. 1b (upper right). Same case on June 5, 1944. There is perhaps a slight clearing of all lesions.

FIG. 2a (lower left). Roentgenogram, taken on January 12, 1944, of M. T. (D-16-A), the control case.

FIG. 2b (lower right). Same case on May 12, 1944. There is possibly a slight clearing.

PLATE 2

the inhibition of the disease in animals (2), was observed to have more toxicity than diasone. Of the 48 cases selected, only 16 (33.3 per cent), including 8 treated and 8 controls, were carried through to the end, whereas of the 58 tuberculous cases in the diasone experiment, 32 (55.2 per cent), including 16 treated and 16 controls, were deemed suitable for reporting. Although many of the cases were rejected because of poor matching rather than because of the effect of the drug, the fact that, for the whole series, the patients were able to tolerate less of the "1048" than diasone speaks for the greater toxicity of the former.

TABLE 4

Condition of 48 cases treated with "1048" six months after the end of the treatment

IMPROVED		UNIMPROVED		DIED		TOTAL
Treated	Controls	Treated	Controls	Treated	Controls	
1	6	11	10	12	8	48

For the 24 patients receiving "1048" a total of 1,737 g. were given in 2,116 days. The daily average per patient, therefore, was 0.8 g. per day. The recovery in the urine was usually higher than that obtained for diasone. Sometimes the urine level was abnormally high and was possibly due to some interfering substance which produced a similar color in the analysis.

The clinical findings are shown in table 4 with a definite unfavorable trend. Only two pairs of cases will be reported in detail. One pair is illustrated in plate 3.

Case Reports

C-4 (O. J.) (table 3) was a 40 year old American male of Jugo-Slav descent who received 61 g. in 122 days. The patient's pulse increased from the beginning of treatment, but he stated that he breathed easier, coughed less and had a better appetite after he began taking the drug. Within a few days after the treatment began he was given a few "A" capsules for a few days (because of a shortage of the "C" type of capsule containing "1048") and he claimed he felt still better. Later, when the "Cs" were begun again he complained of a burning in his esophagus and stomach and developed an intensely blue skin. The dosage was reduced to two and then to one capsule a day. Still later he was put back on two capsules after which he developed "gas pains" and became nervous. His eyes

PLATE 3

Fig. 1a (upper left). Roentgenogram, taken on January 11, 1944, of patient J. K. (C-7) who received 108 grams of "1048" in 108 days.

Fig. 1b (upper right). Same case on May 9, 1944. There is moderate disease progression.

Fig. 2a (lower left). Roentgenogram, taken on January 11, 1944, of J. O'M. (C-7-A), the control case.

Fig. 2b (lower right). Same case on March 18, 1944. There is a slight clearing but the time interval was inadequate for comparative evaluation.

PLATE 3

watered and he complained of "heart burn." Finally he was changed to "A" capsules permanently and almost immediately began to feel better, his skin cleared and he became less nervous. The P. Q. was 304 at the beginning and 234 at the end. The general condition was unchanged after six months. There was a definite toxemic effect of the drug that apparently could be removed only by discontinuing the drug. While the patient did not improve perceptibly, he did not seem to be injured—at least not seriously.

The roentgenological report follows: On January 10, 1944 an extensive fibroid process was present in the right upper lobe. There was a contraction and pulling over of the trachea and a shrinking of the cavity to about half its original size. A slight nodular and infiltrative involvement was present in the left apex. On June 5, 1944 there was a slight increase in the densities in all lung fields.

The control, *C-4-A* (B. Z.) was a 45 year old Polish-American male whose condition was almost exactly like the treated case throughout, except that he did not complain of symptoms and no objective change appeared. His P. Q. changed from 296 to 223. His condition was stationary after six months. The roentgenogram on January 7, 1944 revealed a slight involvement in both apices containing a few tiny cavities, and on May 9, 1944 a slight clearing.

The last pair of cases in table 3 is also shown in plate 3.

C-7 (J. K.) (table 3, and plate 3, figures 1a and 1b) was a 22 year old Irish-American male who received 108 g. of drug in 108 days. The patient complained of gas pains, headache and slight nausea at first, but these mild symptoms disappeared until near the end of the experiment when he began to have blood-streaked sputum. He was then taken off the treatment. The P. Q. changed from 397 to 353. The roentgenograms revealed the following: On January 11, 1944 there were many small cavities in the right upper lobe surrounded by infiltrations. The process extended down almost to the middle of the lung. There was a cluster of tubercles in the left apex extending into the subclavicular area, and a few scattering tubercles down to the mid-field (plate 3, figure 1a). On May 9, 1944 there was an extension of the process in the right upper lobe with more infiltration. Also there was an increase of density in the left lung. The process extended downward to a point near the mid-field (plate 3, figure 1b). Six months after the treatment the process was stationary.

C-7-A (J. O'M.)(table 3, and plate 3, figures 2a and 2b) was a 25 year old Irish-American male who did not notice any change in his condition as a result of the treatment. Towards the end of the observation period a thoracoplasty was done. His P. Q. changed from 386 to 226 before the operation and six months later he was much improved.

This case illustrates the unpredictable aspect of tuberculosis. For no known reason this patient improved more rapidly than the treated case. On January 11, 1944 a large fibroid process was present in the left apex with extension down to the lower third with infiltrative and scattered acinous-nodose tuberculosis. There was a considerable contraction and pulling over of the trachea to the left. A mild involvement was present in the right upper with partially healed discrete lesions. On March 18, 1944 very little change was noted.

The total demerit figures for the "1048" treated cases were 3,860 before and 3,810 after the treatment, a negligible change The control cases, however, changed from a 3,800 total to 3,490, a slightly favorable result.

There were no patients who were entirely symptom-free after taking "1048." A few, however, had such slight reactions that they could continue the drug

without interruptions. A few were "rested" for a while and then treatment was resumed. Practically all complications were found contraindications to the treatment. Two patients with mild diabetes became worse as a result of the treatment with "1048." One case with peptic ulcers reacted badly and had to be taken off the treatment. A case of pernicious anemia seemed to tolerate "1048" very well, for his hemoglobin was not unduly depressed. The effect on the tuberculosis, however, was nil. In spite of the negative effect on this one case of pernicious anemia, such treatment is surely contraindicated in the disease.

COMMENT

Since the clinical results of these experiments are self-evident, the discussion can be limited to possible controversial issues. A question may legitimately be raised as to the propriety and dependability of the "handicapping system" of checking clinical work. For most clinical studies, such a system may not be necessary, but it is especially useful where progress is only slight or questionable. The chief value is that it affords an opportunity to match cases more closely than can be done by other objective and subjective means. Then, when carefully used, it gives an assuring impersonal check on the classical methods of evaluation. While all the factors selected may not have much value in appraisal of the intrinsic changes in any patient, there are some that are quite stable and dependable. The best example of the latter is perhaps the various blood proteins.

Another question might be raised as to why the "fixed" factors were used at all? If two people are exactly alike in all details it wouldn't be necessary to use them. When it becomes necessary to compare patients of widely different types, they help to make a better comparison.

Finally, it must be admitted that the method as used may be needlessly detailed. Since all calculations were applied alike in every case, and since every factor seemed to contribute to a more accurate result, nothing was altered after the experiment was begun.

The selection of cases, the matching of the cases and every step taken during the course of the experiment were done by workers without any knowledge of the results of others, the type of treatment or the dosage of the drug. Only when the final figures and findings were assembled did anyone know the results of the other workers. The status of the treated cases alone at the end of the experiment therefore can be accepted as a negative result or in some cases a worse result than would have occurred under ordinary treatment without a drug. In addition, the matched controls which fared as well or better than the treated cases give the whole result an absolutism that is unequivocal and final.

SUMMARY

A series of 53 patients with far advanced tuberculosis was treated with sulphone compounds. Every patient was matched as closely as possible with a similar patient who was given a placebo in the guise of the drug.

Treatment was begun with diasone on 29 of the patients but only 16 were carried to the completion of the experiment. Treatment was started in 24 patients with "1048" but only 8 were carried to the completion of the experiment.

The "incomplete" cases consisted of those in which death, accident or other incidents broke up the pairs before completion; in which obscure complications, overlooked at first, were discovered; in which complications developed which required taking the patients off the special treatment or in which the matching was poor.

The results of the treatment with both drugs were essentially negative so far as favorable effects on the disease tuberculosis were concerned. A few cases appeared to be injured by the treatment. The symptoms of peptic ulcers and diabetes were aggravated by both drugs. In a patient with lung abscess treated by mistake with diasone, the abscess improved but diabetes developed during the treatment. Albumin in the urine was increased in a few patients treated with both drugs, although about half as many controls also had increased albumin.

In an analysis after six months' time, the diasone-treated patients and their controls ran parallel. There were 5 improved treated cases and 4 improved controls, while there were 14 unimproved treated and 11 unimproved controls, 10 dead treated cases and 15 dead controls.

In the "1048" group, one treated patient improved while 6 controls improved; 11 treated cases were unimproved while 10 controls were unimproved, and 12 treated cases died while 8 controls died.

A numerical handicapping system was also used to evaluate the prognosis of each patient. Factors for age, race, sex, constitution, quantity and quality of the disease, as determined by clinical, roentgenological and laboratory methods, were used in matching.

Of the completed treated cases, the 16 cases receiving diasone had a total of 8,470 demerit points before and 8,740 after the treatment, a loss of 270 points. The matched controls had the same after as before the experiment, namely, 8,200 points. The net loss of the treated cases was well within the limits of experimental error.

In the "1048" group there was a gain of 50 points in 3,860 points in the treated group, but a gain of 310 points in 3,800 points of the control group.

The best that can be said, therefore, for diasone as a treatment of *advanced pulmonary tuberculosis* is that it may not cause injury to patients when the toxic effects are carefully watched. In certain cases treated with "1048" a definite and permanent injury seemed to result. By none of the known means of evaluation could a beneficial effect be observed with either drug.

The negative results in this series, however, do not prove that any or all earlier types of cases may not be benefited, nor should our findings discourage further attempts to find a chemotherapeutic agent for a treatment of the disease.

SUMARIO

A una serie de 53 tuberculosos muy avanzados se les trató con compuesto de sulfona y para cada enfermo se tomó otro lo más semejante posible, que recibió un placebo en vez de la droga.

En 29 enfermos se comenzó el tratamiento con diasona, pero sólo en 16 se completó el experimento. En 24 se inició la terapéutica con "1048", pero solamente en 8 se completó el experimento. Los casos "incompletos" comprendieron aquéllos en que la muerte o algún incidente rompieron las parejas antes de terminar el estudio; aquellos en los que se descubrieron complicaciones oscuras inadvertidas al principio y aquéllos en que se presentaron las complicaciones que obligaron a suspender el tratamiento especial o en los que el apareamiento era deficiente.

Los resultados del tratamiento con ambas drogas fueron esencialmente negativos en cuanto a efecto favorable sobre la tuberculosis. Unos pocos casos fueron aparentemente perjudicados por el tratamiento. Los síntomas de úlceras pépticas y diabetes fueron agravados por ambas drogas. En un enfermo con absceso pulmonar, tratado por error con diasona, el absceso mejoró pero se presentó diabetes durante el tratamiento. La albuminuria aumentó en algunos enfermos tratados con ambas drogas, aunque aproximadamente en la mitad de los testigos también aumentó la albúmina.

En un análisis ejecutado al cabo de seis meses, los enfermos tratados con diasona y sus testigos mostraron paralelismo, pues hubo mejoría en 5 casos tratados y en 4 testigos y, en cambio, no lo hubo en 14 de los tratados y en 11 testigos y murieron 10 de los casos tratados y 15 de los testigos.

En el grupo tratado con "1048" mejoraron uno de los tratados y seis testigos; y no 11 de los tratados y 10 testigos y murieron 12 de los tratados y 8 testigos.

También se usó un sistema numérico de clasificación para avaluar el pronóstico de cada paciente, tomando en cuenta los factores de edad, raza, sexo, constitución, cantidad y calidad de la enfermedad, determinadas por los métodos clínicos, roentgenológicos y de laboratorio.

De los casos hasta el fin del experimento, los 16 que recibieron diasona tenían 8,470 puntos de demérito antes y 8,740 después del tratamiento, o sea, una pérdida de 270 puntos. Los testigos mostraron los mismos tanto después como antes del experimento, a saber, 8,200 puntos. La pérdida neta de los casos tratados correspondió bastante bien a los límites de un error experimental.

En el grupo "1048" hubo una ganancia de 50 puntos en 3,860 puntos en el grupo tratado, comparados con 310 puntos de ganancia en 3,800 puntos del grupo testigo.

Lo más que puede decirse, por lo tanto, sobre la diasona como tratamiento de la *tuberculosis pulmonar avanzada*, es que puede que no resulte nociva para los enfermos si se vigilan cuidadosamente los efectos tóxicos. En ciertos casos tratados con "1048" observose un efecto nocivo bien aparente y permanente. Con ninguno de los medios de evaluación conocidos pudo observarse efecto beneficioso con una u otra droga.

Sin embargo, los resultados negativos obtenidos en esta serie no demuestran que no pueda beneficiarse alguno o todos los tipos tempranos de casos, ni tampoco deben desalentar estos hallazcos nuevos esfuerzos encaminados a encontrar un agente quimioterapéutico contra la enfermedad.

REFERENCES

(1) Sher, Ben C., and Kloeck, John M.: The combined action of P,P′-diaminodiphenylsulfone and immunization in experimental tuberculosis, Am. Rev. Tuberc., 1946, *53*, 250.

(2) Sweany, Henry C., Sher, Ben C., and Kloeck, John M.: Derivatives of P-P′-diaminodiphenylsulfone and sulfanilamide in experimental tuberculosis, Am. Rev. Tuberc., 1946, *53*, 254.

(3) Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: Effect of promin (sodium salt of P-P′-diaminodiphenylsulfone-N,N′ dextrose sulfonate) on experimental tuberculosis: A preliminary report, Proc. Staff Meet., Mayo Clin., 1940, *15*, 695.

(4) Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: The treatment of experimental tuberculosis with promin (sodium salt of P,P′-diaminodiphenylsulfone-N,M′-dextrose sulfonate): A preliminary report, Proc. Staff Meet., Mayo Clin., 1941, *16*, 187.

(5) Hinshaw, H. C., and Feldman, W. H.: Treatment of experimental tuberculosis: Use of sodium P,P′-diaminodiphenylsulfone-N,N′-dextrose sulfonate (promin) with notes on some toxic effects observed in man, J. A. M. A., 1941, *117*, 1066.

(6) Feldman, W. H., Hinshaw, H. E., and Moses, H. E.: Promin in experimental tuberculosis: Sodium P,P′-diaminodiphenylsulfone N,N′-dextrose sulfonate, Am. Rev. Tuberc., 1942, *45*, 303.

(7) Feldman, W. H., Mann, F. C., and Hinshaw, H. C.: Promin in experimental tuberculosis: Observations on tuberculous guinea pigs before and after treatment with sodium P,P′-diaminodiphenylsulfone-N,N′-dextrose sulfonate (promin), Am. Rev. Tuberc., 1942, *46*, 187.

(8) Medlar, E. M., and Sasano, K. T.: Promin in experimental tuberculosis in the guinea pig, Am. Rev. Tuberc., 1943, *47*, 618.

(9) Smith, M. I., Emmart, E. W., and Westfall, B. B.: Action of certain sulfonamides, sulfones and related phosphorus compounds in experimental tuberculosis, J. Pharmacol. & Exper. Therap., 1942, *74*, 160.

(10) Steenken, W., Heise, F. H., and Wolinsky, C.: Treatment of experimental tuberculosis in the vaccinated and nonvaccinated guinea pig with promin, Am. Rev. Tuberc., 1943, *48*, 453.

(11) Steinbach, M. M., and Duca, C. J.: Promin (diaminosulfone derivatives) in experimental tuberculosis, Proc. Soc. Exper. Biol. & Med., 1942, *49*, 460.

(12) Barach, A. L., Molomut, N., and Soroka, M.: Inhalation of nebulized promin in experimental tuberculosis, Am. Rev. Tuberc., 1942, *46*, 268.

(13) Tytler, W. H.: Sulphone compounds in the chemotherapy of tuberculosis: A review of experimental results and pharmacological data: Therapeutic results in experimental tuberculosis, Tubercle, 1944, *25*, 95.

(14) Callomon, F. F. T.: New derivatives of diaminodiphenylsulfone: Their therapeutic effect in experimental tuberculosis of guinea pigs, Am. Rev. Tuberc., 1943, *47*, 97.

(15) Feldman, W. M., Hinshaw, W. C., and Mann, F. C.: Promizole in tuberculosis, Am. Rev. Tuberc., 1944, *50*, 418.

(16) Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: The effects on experimental tuberculosis of 4,4′-diaminodiphenylsulfone, Am. J. M. Sc., 1944, *207*, 290.

(17) Tytler, W. H.: Sulfone compounds in the chemotherapy of tuberculosis: A review of experimental results and pharmacological data: Bacteriostasis action and bacteriocidal action in vitro, Tubercle, 1945, *26*, 23.

(18) Hinshaw, H. C., Pfuetze, Karl, and Feldman, W. H.: Treatment of tuberculosis with promin, Am. Rev. Tuberc., 1943, *47*, 26.

(19) Petter, C. K., and Prenzlau, W. S.: Treatment of tuberculosis with diasone, Am. Rev. Tuberc., 1944, *49*, 308.

(20) FAGET, G. H., PAGGE, R. C., JOHANSEN, F. A., DINAN, J. F., PREJEAN, B. M., AND ECCLES, C. G.: The promin treatment of leprosy, Pub. Health Rep., 1943, *58*, 1729.

(21) HEAF, F. R. C., HURFORD, J. V., EISER, A., AND FRANKLIN, L. M.: Tuberculosis treated with promin, Lancet, 1943, *1*, 702.

(22) WILLIS, H. S.: Discussion: Treatment of tuberculosis with promin, Am. Rev. Tuberc., 1943, *47*, 33.

(23) HIGGINS, G. M.: Toxic effects of promin (sodium P,P'-diaminodiphenylsulfone N,N'-didektrose sulfonate) on the erythrocytes of guinea pigs, Am. J. M. Sc., 1943, *205*, 834.

(24) CORPER, H. J., AND COHN, M. L.: The use of diasone for the treatment of tuberculosis, J. A. M. A., 1945, *127*, 1043.

(25) DANCY, R. J., SCHMIDT, R. H., AND WILKIE, J. M.: Promin in pulmonary tuberculosis, Am. Rev. Tuberc., 1944, *49*, 510.

(26) JOHNSON, R. M.: Absence of toxic manifestations following the parental administration of promin, J. A. M. A., 1940, *114*, 520.

(27) ZUCKER, G., PINNER, M., AND HYMAN, H. T.: Chemotherapy of tuberculosis: Promin by the intravenous drip method, Am. Rev. Tuberc., 1942, *46*, 277.

(28) HINSHAW, H. C., FELDMAN, W. H., AND PFUETZE, K. H.: The clinical administration of 4,2'-diaminophenyl-5'-thiazolesulfone (promizole) in tuberculosis: A preliminary report, Proc. Staff Meet., Mayo Clin., 1944, *19*, 33.

(29) BRAEUNING, H.: Der Beginn der Lungentuberkulose beim Erwachsenen, Leipzig, 1938.

(30) HINSHAW, H. C., AND FELDMAN, W. H.: Evaluation of chemotherapeutic agents in clinical tuberculosis, Am. Rev. Tuberc., 1945, *50*, 202.

(31) SWEANY, H. C., CLANCY, C. L., RADFORD, M. H., AND HUNTER, V.: Body economy of vitamin C in health and disease with special studies in tuberculosis, J. A. M. A., 1941, *116*, 469.

(32) LURIE, MAX B.: Experimental epidemiology of tuberculosis hereditary, J. Exper. Med., 1944, *79*, 573.

(33) AGUILAR, OSCAR P., AND SIRLIN, GREGARIO: La Constitution Individual en la Tuberculosis, Publicaciones del centro de Investigaciones Tisiologicas, V. 7, 1943, pp. 7–124.

VIRULENCE OF TUBERCLE BACILLI[1]

In Vitro Testing by the Use of Diphtheria Antitoxin

PHILIP F. WAGLEY AND W. STEENKEN, JR.

There have appeared in the literature of the past few years several papers indicating the possibility of specific relationships between diphtheria antitoxin and *Mycobacteria tuberculosis.* In 1926, Wolff (1) reported some clinical improvement in a series of tuberculous cases treated with diphtheria antiserum. Because of certain similarities between the tubercle bacillus and some of the diphtheroids, Schain *et al.* (2, 3) have studied the effects of diphtheria antitoxin on *Mycobacteria tuberculosis in vitro* and *in vivo*. These observations led to experiments (4) alleged to give an *in vitro* method of determining the degree of virulence of any strain of tubercle bacillus. This conclusion, if true, is important both for prognostic purposes in clinical work and as a premise on which to study the basic mechanisms of the virulence of *Mycobacteria tuberculosis.* Therefore, we made the following experiment.

MATERIALS

The procedure outlined previously by Schain (4) was followed.

1. *Culture medium:* 1,000 g. of finely diced potatoes were mixed with 120 cc. of glycerin and 1,000 cc. of water and autoclaved at 15 lbs. pressure for one-half hour. The fluid was filtered through cotton and gauze; 1,500 cc. of 0.6 per cent salt solution and 40 g. of agar were added to 500 cc. of the above extract. This was heated in a water bath until the agar was in solution. The pH was adjusted to 7.4. The medium was tubed in 4 cc. quantities and autoclaved at 20 lbs. pressure for fifteen minutes. The tubes were then cooled to 55°C. and to each was added 1 cc. of human blood[2] or of a mixture of human blood and antitoxin (warmed to 37°C.). The tubes were then rotated for thorough mixing, slanted and cooled.
2. *Diphtheria antitoxin* (obtained from the Board of Health, New York City, Lot No. 838) containing 1,200 units of diphtheria antitoxin per cc. and 1:10,000 merthiolate was used.
3. *Normal horse serum,* containing merthiolate in a concentration of 1:10,000, served as the control for diphtheria antitoxin.
4. *Citrated human blood* (100 cc. of 2.5 per cent solution of sodium citrate and 500 cc. of human blood) was collected from a case of inactive tuberculosis.
5. The following microörganisms were used for the tests:
   (A) Virulent for guinea pigs
      Strain 1:(H37 Rv) virulent dissociant (5)
      Strains 2 through 7 (virulent tubercle bacilli recently isolated from patients' sputa)[3]
      Strain 8:(Pl. fl.—Rv)[3]

[1] From the Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.

[2] The blood was obtained from an arrested case of minimal tuberculosis, who failed to react to an intracutaneous injection of a 1:10,000 dilution of Old Tuberculin.

[3] Pathogenicity tested by animal inoculation.

(B) Avirulent for guinea pigs (6)
Strain 9: (H37 Ra) avirulent dissociant
Strain 10: (R1 resistant) avirulent dissociant
Strain 11: (H4 Ra) avirulent dissociant
Strain 12: (J. H. 16 Ra) avirulent dissociant
Strain 13: (J. H. 6 Ra) avirulent dissociant
(C) Saprophytic
Strain 14: (*M. Phlei*)

Procedure: Four weeks growths of each of the above strains were removed from culture slants and ground in sterile mortars. Uniform suspensions were then made in physiological saline and centrifuged at low speed for five minutes to remove any large clumps of tubercle bacilli. To determine the concentration of the different suspensions 1 cc. of each was transferred to a weighed watch glass and evaporated to dryness on a water bath. The watch glass and contents were weighed and the dry weight of tubercle bacilli was determined. The remaining portion of each suspension was then diluted with saline so that 0.5 cc. was equivalent to 0.66 mg. dry weight of microörganisms.

Each strain of tubercle bacilli was then tested in duplicate by seeding it on 13 different slants of the above medium containing various concentrations of antitoxin and merthiolate with appropriate controls. The first set contained 12 units of diphtheria antitoxin per cc. of media, the second set 24 units, and so on, increasing the concentration of antitoxin by 12 units per cc. of media until a concentration of 120 units per cc. was reached. Control series of merthiolate-horse-serum-control media were also prepared by adding these ingredients to the medium in concentrations equivalent to those present in the tubes containing 48, 84, 120 units per cc. of diphtheria antitoxin. A third set, a medium control, contained neither antitoxin nor merthiolate.

Each series was then seeded with 0.5 cc. of the suspensions. The tubes were sealed with melted paraffin; needle puncture was made in each seal for gas exchange. The tubes were left in an inclined position for several hours so that excess moisture could be absorbed by the media. They were then incubated in an upright position at 37.5°C.

Growth recordings were made at the end of four days, two weeks, three weeks and six weeks.

RESULTS

As indicated in chart 1, growth of all strains of tubercle bacilli under test was inhibited by the addition of a sufficient concentration of diphtheria antitoxin. However, the amounts necessary to inhibit growth of virulent organisms are not consistently greater than those preventing growth of nonvirulent dissociants.

The saprophyte, *M. Phlei,* reached approximately maximum growth at the end of four days in all tubes except those containing 120 units of antitoxin per cc. The growth was less rapid in that concentration and it required three weeks to reach more or less maximum extent. It will be noted also in this experiment that, on an average, at least twice as much antitoxin was required to inhibit the growth of the virulent strains of tuberlce bacilli as has been reported elsewhere (4).

DISCUSSION

Schain (4) has reported that the "virulence of tubercle bacilli may be measured *in vitro* by the extent to which the bacilli are inhibited in their growth by diph-

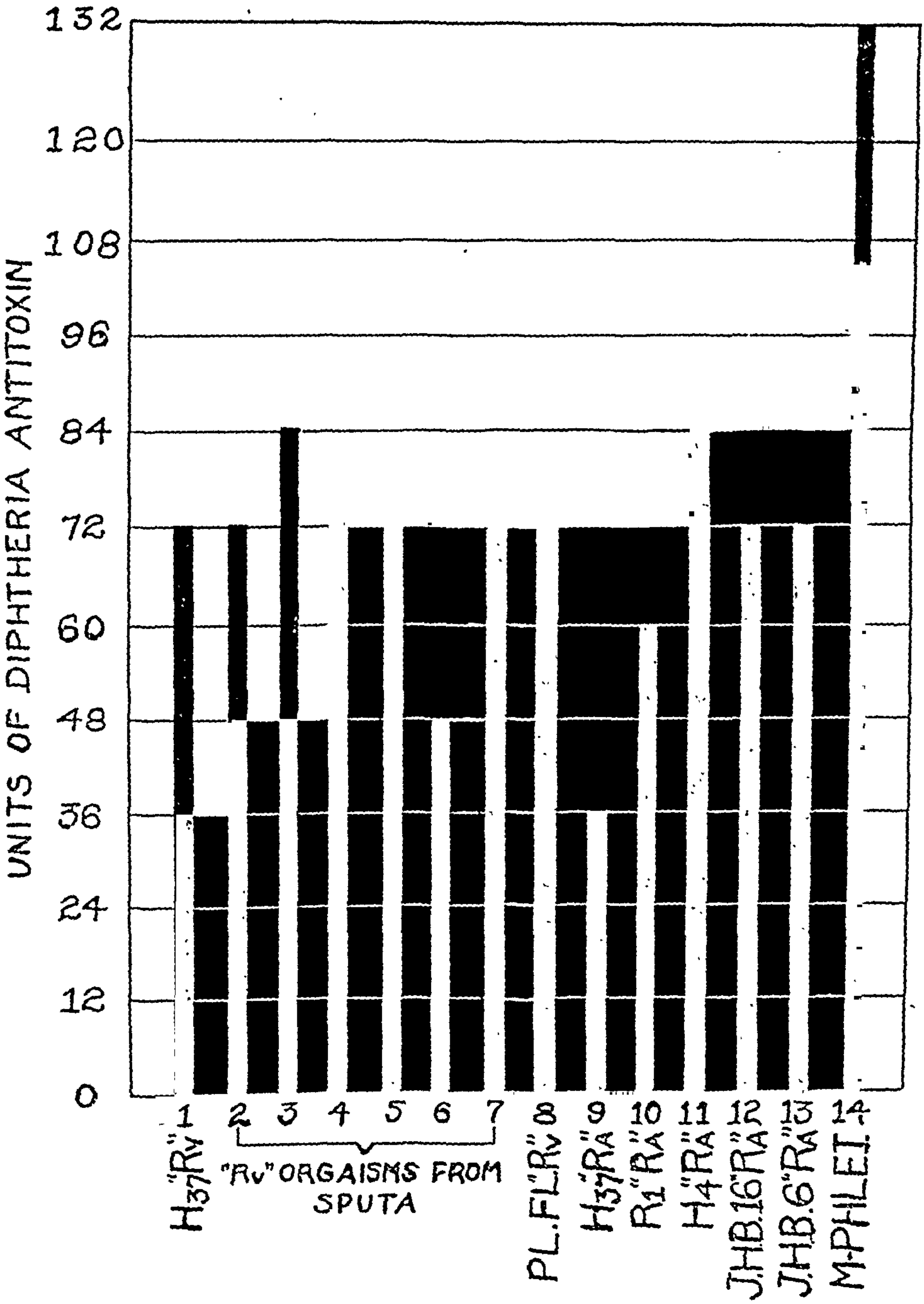


CHART 1. Units of diphtheria antitoxin necessary to completely prevent growth of acid-fast bacilli.

theria antitoxin," and "the amount of diphtheria antitoxin necessary to prevent the growth of tubercle bacilli appears to be inversely proportional to their virulence." In our experiment, however, neither the virulent nor avirulent strains of human tubercle bacilli were inhibited as a group by any particular concentration

of diphtheria antitoxin. In other words, the effective inhibiting concentration of antitoxin varied from one strain to another and over a wide range, irrespective of virulence. There were no marked zones of inhibition produced by the antitoxin that would act as a basis for differentiating between virulent and avirulent human tubercle bacilli.

The blood used in these tests was taken from a person with minimal inactive tuberculosis, but this factor was apparently not responsible for irregularities in the inhibitory action of the diphtheria antitoxin. The rate of growth of the virulent human microörganisms on the control media, as ordinarily observed, was much more rapid than that of the avirulent ones (*M. Phlei* excepted); and the amount of growth of the virulent microörganisms at the end of six weeks was indistinguishable from that of the avirulent strains. We have checked still further by repeating the same experiment on a much smaller scale but using blood of a normal person. The results were essentially the same as those that have been described.

CONCLUSIONS

1. Diphtheria antitoxin in certain concentrations inhibits the growth of both virulent and avirulent forms of human tubercle bacilli.
2. In our hands, diphtheria antitoxin has proved to be valueless in measuring differences in virulence of strains of human tubercle bacilli.
3. Under the conditions of the experiment, diphtheria antitoxin has only affected the growth of the saprophyte, *M. Phlei*, in very high concentrations.

CONCLUSIONES

1. La antitoxina diftérica a ciertas concentraciones inhibe el desarrollo de las formas tanto virulenta como avirulenta de los bacilos tuberculosos humanos.
2. A los autores, la antitoxina diftérica no les resultó útil para medir las diferencias de virulencia entre cepas de bacilos tuberculosos humanos.
3. En las condiciones del experimento descrito, la antitoxina diftérica sólo afectó el desarrollo del saprófito, *M. Phlei*, a concentraciones altísimas.

REFERENCES

(1) WOLFF, S. B.: The antagonistic effects of antidiphtheritic serum on the tubercle bacillus, New Orleans M. & S. J., 1926–27, *79*, 353.

(2) SCHAIN, P., AND PETROFF, S. A.: The inhibitory action of diphtheria antitoxin on the growth of the tubercle bacillus, Quart. Bull. Sea View Hosp., 1940, *5*, 432.

(3) GERSHENFELD, L., AND SCHAIN, P.: Modification of the tubercle bacillus treated with diphtheria antitoxin, Quart. Bull. Sea View Hosp., 1942, 7, 400.

(4) SCHAIN, P.: Virulence of tubercle bacilli: *in vitro* method for its estimation, Am. Rev. Tuberc., 1944, *49*, 551.

(5) STEENKEN, W., JR., OATWAY, W. H., JR., AND PETROFF, S. A.: Biological studies of the tubercle bacillus. III. Dissociation and pathogenicity of the R and S variant of the human tubercle bacillus H37, J. Exper. Med., 1934, *60*, 515.

(6) STEENKEN, W., JR., AND GARDNER, L. U.: Vaccinating properties of avirulent dissociates of five different strains of tubercle bacilli, Yale J. Biol. & Med., 1943, *15*, 393.

PERIODICALS DEVOTED TO TUBERCULOSIS IN THE UNITED STATES OF AMERICA

ROBERT G. PATERSON[1]

As one examines a current number of the *American Review of Tuberculosis*, there is a definite sense of satisfaction and pride that the tuberculosis movement in the United States has achieved a journal of such widely acclaimed scientific standing.

Present day readers of the *Review* take for granted its regular monthly appearance. After a continuous run of twenty-seven years such an attitude is warranted. However, the establishment of this record was not without its early trials, nor was it the first periodical in the United States devoted exclusively to tuberculosis. There is evidence of at least 7 such journals preceding the *Review*.

The attempt to trace the filiation of the periodicals devoted to tuberculosis in the United States follows a broken and tortuous path. Aside from the nation-wide sources, such as the *Transactions* of the American Medical Association (1–33, 1848–1882//)[2] and its *Journal* (V. 1, 1883 +), the *Reports and Papers* of the American Public Health Association (1–37, 1873–1912//) and its *Journal* (V. 1, 1911 +), *The Sanitarian* (V. 1–52, 1873–1904//), and the *Transactions* of the American Clinical and Climatological Association (1, 1884 +), where various phases of the tuberculosis problem were discussed, there were several attempts to establish a journal devoted exclusively to tuberculosis.[3] Most of these ventures were short-lived. Yet they afford important sources of information concerning the early efforts to attack this major disease problem, both from the standpoint of the medical profession and of society at large.

1899—Medico-Legal Journal—New York: With Volume 17, No. 2, September, 1899, the *Medico-Legal Journal*[4] began devoting a portion of its pages to the problem of tuberculosis. It was published quarterly by the Medico-Legal

[1] Secretary, Committee on Archives, National Tuberculosis Association.

[2] Symbols used: + publication current; // publication ended.

[3] There were several foreign periodicals devoted exclusively to tuberculosis which antedated or appeared about the same time as the first American periodicals. These were:

1887 Études expérimenteles et cliniques sur la tuberculose, Paris.
1891 Tubercolosi, (bi-monthly), Milan.
1893 Revue de la tuberculose, (quarterly), Paris.
1900 Oeuvre antituberculeuse, Paris.
1900 Zeitschrift für Tuberkulose und Heilstättenwesen, Leipzig.
1901 Tuberculosis, The Journal of the National Association for the Prevention of Consumption and Other Forms of Tuberculosis, (monthly), London.
1902 Monatsschrift des Internationalen Centralbureaus zur Bekämpfung der Tuberculose, Leipzig.
1903 Beiträge zur Klinik der Tuberculose, Würzburg.
1904 Bulletin de la Ligue contre la Tuberculose en Touranie, (bi-monthly), Tours.

[4] The Medico-Legal Journal, V. 1–50, No. 1, June, 1883 to V. 50, No. 3, May–June, 1933, New York, New York. V. 1–32 published under auspices of the Medico-Legal Society of New York and included its transactions.

Society of New York. The editor was Clark Bell.[5] It recorded the transactions of the American Congress on Tuberculosis (1900–1913) the first organized attempt to grapple with tuberculosis on a national scale.[6] It printed many original articles dealing with the disease. After 1904, the year the National Tuberculosis Association was organized, the Journal's interest in tuberculosis, as revealed by articles and comment, waned and finally ceased in 1914. This was the first periodical in the United States to espouse the cause of tuberculosis both from the standpoint of treatment as well as prevention.

1899—Journal of Tuberculosis—Asheville, North Carolina.: At Asheville, North Carolina, Dr. Karl von Ruck[7] began the publication of *The Journal of Tuberculosis*[8] in 1899. It was a quarterly magazine devoted to the prevention and cure of tuberculosis. The subscription price was one dollar per year. Volume 1, No. 1, was issued in January, 1899. The purpose of the Journal was "what is hoped to be the gradual establishment of a representative publication of American endeavor and progress in dealing with the prevention and cure of tuberculosis." . . . "It is the purpose of the editor not only to give his own views and experiences, but to obtain original communications from others, to republish in full or by abstract, all important communications on tuberculosis to current medical literature both in Europe and America, and in the editorial columns to freely discuss their respective merits."[9] The Journal ceased publication with Volume 5, No. 4, October, 1903. Unfortunately, there was no editorial indicating the reasons for the cessation. As one examines these five volumes, the conviction grows that this Journal comes more nearly presaging the *American Review of Tuberculosis* than any of those which came upon the scene.

1900—Tubercle—Chicago, Illinois: In April, 1900, Dr. Thomas Bassett Keyes[10] became editor of *Tubercle*, a monthly journal and review of tuberculosis. It was published at Chicago, Illinois and was the successor to *The Journal of the American Psychological, Medical and Surgical Society*. This journal began in October, 1897, and continued as such to March, 1900. *Tubercle* began with Volume 4, No. 1, April, 1900 and finally ceased publication with Volume 5, No. 3, December, 1900.

The subscription price was one dollar *per annum*. The number of pages varied from 16 to 32. Its contents consisted of articles copied from the current medical

[5] Clark Bell (1832–1918) lawyer. Took up practice in New York City in 1864, was editor and publisher of Medico-Legal Journal 1883–1916. President Medico-Legal Society of New York for sixteen terms. Founder American Congress on Tuberculosis.

[6] See: Robert G. Paterson, Ph.D.: Antecedents of the National Tuberculosis Association, Historical Series No. 2, National Tuberculosis Association, New York, 1945.

[7] Karl von Ruck (1849–1922) physician. Founder and medical director Winyah Sanatorium, Asheville, North Carolina, 1888–1910. Education in Germany and M.D. from University of Michigan. Postgraduate work with Virchow and Koch. Was present March 24, 1882 when Koch announced the discovery of the tubercle bacillus.

[8] V. 1–3 were edited by Karl von Ruck; V. 4–5 were edited by Karl and Silvio von Ruck.

[9] op. cit. p. 1.

[10] Thomas Bassett Keyes (1874–1938) physician. Chairman of first organization committee American Congress on Tuberculosis.

journals. It was also the medium for the American Health Resort Association as well as the Forum of Tuberculosis, Climatology and Hydrology which had their headquarters in Chicago.

A review of its pages leaves the definite impression that the journal was founded with the express purpose of supporting the idea of climate, especially that of northern Wisconsin, in the treatment of tuberculosis. Doctor Keyes had established a health camp for the tuberculous at Butternut, Wisconsin. There was also open advocacy of certain drugs in the treatment of the disease.

It is not surprising therefore, because of its motivation, that the life of the periodical was brief.

1904—Journal of the Outdoor Life—New York: Dr. Lawrason Brown[11] of Saranac Lake, New York began the publication of *The Outdoor Life* in February, 1904. It was a monthly and was published at the Adirondack Cottage Sanitarium (*sic*), Saranac Lake, New York. The subscription price was one dollar per year. The purpose of the journal was "to be helpful to all persons leading an outdoor life for their health, but particularly to be of assistance to the vast army of persons who are suffering from pulmonary tuberculosis, which is preventable and curable—curable not by patent medicines but only by plenty of fresh air, rest at first and an abundance of nourishing food."

At a meeting of the Executive Committee of the National Tuberculosis Association held on January 9, 1905, Dr. Hermann Michael Biggs (1859–1923), of New York City, moved "that if suitable arrangements could be made with the publishers of *The Outdoor Life* the paper should be hereafter sent to all members of and contributors to the National Tuberculosis Association."[12]

Beginning with Volume 2, No. 1, February, 1905, the name was changed to the *Journal of the Outdoor Life*. It was published monthly at Saranac Lake, New York by the Journal of the Outdoor Life Publishing Company of which Doctor Brown was president, secretary and treasurer.

With Volume 3, No. 3, April, 1906, the journal became the official organ of the National Tuberculosis Association. Three years later, with Volume 7, No. 1, January, 1910, the journal was published at New York City as the official organ of the National Tuberculosis Association by a newly incorporated Journal of the Outdoor Life Publishing Company. Dr. James Alexander Miller, New York City, was president; Dr. Livingston Farrand (1867–1939) vice-president and treasurer; and Warwick S. Carpenter, secretary and managing editor. Carpenter was succeeded by Philip P. Jacobs, Ph.D. (1879–1940) as secretary and managing editor, with Volume 8, No. 5, May, 1911.

This arrangement continued until Volume 19, No. 9, September, 1922, when the National Tuberculosis Association bought out the publishing company and became sole owner of the journal. The editorial staff consisted of James Alexander Miller, M.D., editor-in-chief, and Philip P. Jacobs, Ph.D., managing editor,

[11] Lawrason Brown (1871–1937) physician. Resident physician Trudeau Sanatorium 1901–1912. Instructor Trudeau School of Tuberculosis 1914–1937.

[12] Minute Book, National Tuberculosis Association, 1904–5, pp. 91–92.

and eleven other editors scattered throughout the country. Doctor Miller resigned as editor-in-chief with Volume 26, No. 8, August, 1929.

With Volume 26, No. 9, September, 1929, the management was confided to an editorial board of fourteen members and Doctor Jacobs as managing editor. This arrangement continued until Volume 29, No. 6, June, 1932, when Doctor Jacobs was continued as managing editor, Miss Elizabeth Cole as associate editor and S. M. Sharpe as business manager. In September, 1932, Doctor Jacobs became editor and this arrangement continued until the journal ceased publication with Volume 32, No. 12, December, 1935, after thirty-one years of continuous service. Its pages record the tuberculosis movement in this country, especially since 1910.

1905—American Journal of Tuberculosis—Detroit, Michigan: In May, 1905, there appeared *The American Journal of Tuberculosis.* It begun as a monthly and was published at Detroit, Michigan under the editorship of Ernest Lorenzo Shurly, M.D.[13] The journal did not last long. Its life-cycle embraced Volume 1, No. 1, May, 1905 to Volume 1, No. 4, August, 1905. The subscription price was one dollar *per annum.* Its format was excellent and the number of pages was 48 to each number.

The contents consisted of original articles, editorials, news comments and book notices. Doctor Shurly was a high-type educated physician and he put into the periodical a broad viewpoint concerning tuberculosis. Had it not been for a printers' strike in Detroit in August, 1905, it appears likely this journal might have become the tuberculosis periodical of this country. But the strike brought an end to Doctor Shurly's efforts.

1908—Bulletin of the National Tuberculosis Association—New York: In December, 1908 the National Tuberculosis Association began the publication of a mimeographed Confidential Bulletin as a guide to administration of the state and local tuberculosis organizations. As nearly as can be ascertained the issuance of the *Bulletin* between 1908 and 1911 was at irregular intervals. Beginning with the September, 1911 issue it was published monthly. In October, 1914 the *Bulletin* was changed from a mimeographed to a printed form and has continued to the present day.

Beginning with Volume 16, No. 1, January, 1930, Philip P. Jacobs[14] and Elizabeth Cole were carried on the masthead as managing editor and executive editor, respectively. With Volume 22, No. 1, January, 1936, Doctor Jacobs was designated as editor and Miss Cole as associate editor. In Volume 24, No. 7, July, 1938, Doctor Jacobs was carried as editor and Miss Cole's name does not appear. Daniel McCarthy became editor with Volume 25, No. 1, January, 1939. Miss Ellen Lovell was added as assistant editor with Volume 26, No. 5, May,

[13] Ernest Lorenzo Shurly (1845–1913) physician. Associated with Detroit College of Medicine. A pioneer in the field of thoracic surgery. Established at Eloise, Wayne County, first camp in Michigan for the treatment of tuberculosis.

[14] Philip P. Jacobs, Ph.D. (1879–1940) Publicity 1908–11; assistant secretary 1911–20; publicity director 1920–29; publications and extension 1929–38; personnel training and publications 1938–40. National Tuberculosis Association, New York, New York.

1940. With Volume 29, No. 7, July, 1943, Miss Lovell became editor. Miss Elizabeth Hodgson was added as associate editor with Volume 30, No. 11, November, 1944.

The Monthly Bulletin is the best single record available for the specific facts with respect to the development of the tuberculosis movement in the United States of America.

1915—Anti-Tuberculosis Bulletin—Manila, Philippine Islands: In January, 1915, Volume 1, No. 1, there appeared a tuberculosis journal published quarterly by the Philippine Island Anti-Tuberculosis Society at Manila entitled *Anti-Tuberculosis Bulletin.* It was printed in English, Spanish, and Tagalog languages. Dr. Jose Fabella was listed as secretary and managing editor with the initial number and continued to December, 1916, Volume 2, No. 12. Beginning with Volume 2, No. 1–4, April, 1916, the Bulletin was issued as a monthly. With Volume 3, No. 1, March, 1917, it reverted to a quarterly and Dr. Antonio Hermandez was listed as editor. The Bulletin continued until September, 1920 when it ended with Volume 6, No. 3.

1917—American Review of Tuberculosis—New York: As in the case of the *Journal of the Outdoor Life,* we find that at the organization meeting of the National Tuberculosis Association on June 6, 1904, Dr. John Bessner Huber (1864–1924) of New York City spoke on the advisability of a journal devoted exclusively to the work on tuberculosis.[15] After some discussion Dr. Frederick Forchheimer (1853–1913), of Cincinnati, Ohio, moved "that it is the sense of this meeting that this association shall maintain a journal devoted entirely to the work of the society."[16] While this motion was adopted, yet Dr. Lawrence Francis Flick (1856–1938) of Philadelphia moved "that the question of the maintenance of a journal be left to the Executive Committee with instructions to report back to this Board its conclusions."[17] This report seems never to have been made.

It was not until March, 1917 that No. 1 of Volume 1 of the *American Review of Tuberculosis* made its appearance. It was published monthly at New York City by the National Tuberculosis Association. The purpose was stated as follows: ". . . to offer all who are interested, a medium in which they can present their work and through which they can develop their views."[18]

The editor-in-chief was Dr. Edward Robinson Baldwin of Saranac Lake, New York. The managing-editor was Dr. Allen Kramer Krause[19] of Baltimore, Maryland. There was an editorial board of six men located strategically

[15] Minute Book, National Tuberculosis Association, 1904–5, p. 42.

[16] Another and a major source of tuberculosis information is to be found in the publication of the *Transactions* of the National Tuberculosis Association which began in 1905 and has continued annually to date.

[17] op. cit. p. 48.

[18] American Review of Tuberculosis, V. 1, No. 1, 1917, p. 53.

[19] Allen Kramer Krause (1881–1941) medical research, assistant director Saranac Lake Laboratory 1909–16; director Kenneth Dows Tuberculosis Research Laboratory Johns Hopkins 1916–29; president and director The Desert Sanatorium, Tucson, Arizona, 1929–37; clinical professor medicine Stanford University 1929–37; lecturer Trudeau School of Tuberculosis 1916–29. Trudeau Medal award 1931.

throughout the country. Doctor Krause succeeded Doctor Baldwin as editor with Volume 6, No. 1, March, 1922. Except for changes in the editorial board, the journal continued for seventeen years under this arrangement. With Volume 30, No. 1, July, 1934, Max Pinner, M.D., of Tucson, Arizona, was named assistant to the editor in which capacity he served until Volume 32, No. 1, January 1936.

Doctor Pinner, then at Ithaca, New York, became associate editor with Volume 36, No. 1 in July, 1937, after having taken over the editorial work in March, 1937 on account of Doctor Krause's illness. Finally with the January issue, Volume 41, No. 1, 1940, Doctor Pinner, now of New York City, became editor and Doctor Krause editor emeritus. Doctor Krause served in this capacity until his death in 1941. With Volume 41, No. 1, January, 1940 the *Review* became the official journal of the American Trudeau Society. Beginning with Volume 44, No. 4, October, 1941, the *Review* sought to make its influence more wide-spread by including a summary of each paper in Spanish.

The *Review* has printed almost forty thousand pages of data on tuberculosis since it was established in 1917. During most of the years the National Tuberculosis Association has had to demonstrate its faith in the value of the *Review* by making up publication deficits which, at times, exceeded $15,000 a year. To-day, the *Review* is published at a slight profit and enjoys a wide circulation throughout the world. In fact, during the war years and for those years immediately after peace is established, the full usefulness of the *Review* will be demonstrated as the *only* repository of cumulative information for the guidance of the rebuilders of public health services throughout Europe.

Following the *Review* there have been several other journals devoted exclusively to tuberculosis which have appeared. These have had a more restricted distribution on the whole as compared with the *Review.* However, each of these journals has attempted to fill a specialized need and so has made a contribution to the literature

1935—Diseases of the Chest—El Paso, Texas: In March, 1935, Volume 1, No. 1 of a journal entitled *Diseases of the Chest* began publication at El Paso, Texas. It was the official organ of the Federation of American Sanatoria. Published monthly at two dollars per year, C. M. Hendricks, M.D. of El Paso served as editor-in-chief for Volume 1, No. 1, 1935 to Volume 3, No. 6, June, 1937. On June 7, 1937, the Federation of American Sanatoria became the American College of Chest Physicians. With Volume 3, No. 7, July, 1937, Frank Walton Burge, M.D., Philadelphia, became the editor-in-chief. With Volume 7, No. 8, August, 1941, Ralph C. Matson, M.D.,[20] Portland, Oregon, became editor-in-chief and served in this capacity to the time of his death. With Volume 9, No. 1, January, 1943, the format of *Diseases of the Chest* was changed, the journal was enlarged and published bi-monthly at five dollars per year. Murray Kornfeld, Chicago, has been the managing editor throughout the life of the periodical. There are many articles of value in this journal.

1935—The Quarterly Bulletin of Sea View Hospital—Staten Island, New York:

[20] Died October 26, 1945.

In October, 1935, Volume 1, No. 1, of a journal of tuberculosis and chronic pulmonary diseases entitled *The Quarterly Bulletin of Sea View Hospital* began publication in New York City. It represented the clinical material, discussions and ideas of the staff of Sea View Hospital known as The Clinical Society of Sea View Hospital. The editor was Edwin R. Levine, M.D., assisted by an editorial board varying in number from ten to fourteen members. Published quarterly at two dollars per year, it ran each issue about one hundred twenty pages of material. With Volume 2, No. 3, April, 1937, the publication office was transferred to Staten Island, New York. The price was changed to three dollars per year with Volume 4, No. 2, January, 1939. Publication was suspended for the duration of the war with Volume 7, No. 5, October, 1942.[21]

This journal was of a high order both as to format and content. There were many contributions in the clinical, pathological and X-ray areas. It carried, for example, the important and original ideas of Pol N. Coryllos, M.D.[22] in the field of surgery of pulmonary tuberculosis.

1937—Tuberculology—Denver, Colorado: In May, 1936 there was organized at Kansas City, Missouri, the American Academy of Tuberculosis Physicians. The purpose of the organization was to alleviate the sufferings of the tuberculous and eradicate tuberculosis through scientific pursuits; to elevate the standards of physicians specializing in tuberculosis and allied diseases and to designate those qualified according to the best scientific and practical information available. It holds its annual meeting at the same time and place as the American Medical Association. The headquarters are at Denver, Colorado.

In December, 1937, Volume 1, No. 1 of *Tuberculology* appeared as the official organ of the American Academy of Tuberculosis Physicians. It is a monthly journal of about 28 pages in each issue and is distributed free to members and outstanding libraries throughout the world. The auditor-editor is H. J. Corper, M.D., Denver, Colorado.

CONCLUSION

We have recorded briefly the publication of 11 major periodical sources of information devoted exclusively to presentation of the problem of tuberculosis in the United States. A review of the contents of these journals leaves an impression of great unevenness in material and purpose. The effort to arrive at a high scientific standard of discussion was a long one. The struggle to achieve a wide-spread audience was even more difficult. We believe the record will substantiate the conclusion that, judged from the scientific viewpoint, the *American Review of Tuberculosis* has not only achieved preëminence in the United States but has also carved out for itself a top-ranking place in the literature of tuberculosis throughout the world.

[21] Publication has been resumed as of January, 1946; Edward Robitzek, M.D., Editor.

[22] Pol N. Coryllos (1880–1938) professor of clinical surgery, medical college of Cornell University 1923–1928; director of thoracic surgery at Metropolitan Hospital and Sea View Hospital, New York 1923–38.

CONCLUSIONES

Versa este estudio sobre once importantes fuentes periódicas de información dedicadas exclusivamente a presentar el problema de la tuberculosis en Estados Unidos. Un repaso del contenido de esas revistas deja la impresión de que varían mucho en contenido y propósitos. El esfuerzo realizado para alcanzar un alto nivel científico en la exposición ha sido prolongado y la lucha para alcanzar a un público amplio resultó todavía más difícil. Los datos disponibles comprobarán la conclusión de que, juzgada desde el punto de vista científico, la *American Review of Tuberculosis* no tan sólo ha alcanzado la cúspide en los Estados Unidos, sino que se ha labrado un puesto soberano en la literatura tuberculosa de todo el mundo.

Ralph C. Matson
1880–1945

The name of Ralph C. Matson is in the vanguard of those medical pioneers who opened and developed the field of thoracic surgery. He was that rarity in any profession, a truly great innovator; and those who follow owe him an unpayable debt for what he has accomplished; while those who had the privilege of knowing him personally feel an additional benefit, a greater impetus in their own endeavors from their contact with his buoyant spirit. It is to be hoped that in time a biographer for Ralph Matson will appear; for his achievements, his history and his personality are all equally good material for a legend, a true American legend of individual achievement with color and action and humor enough to carry the reader, with little help from the author.

Ralph Charles Matson was born in Brookville, Pennsylvania, in 1880. His family moved to Oregon in his childhood. As a young man he attended and in 1902 graduated from the University of Oregon Medical School with his twin brother, Ray. Thereafter he took postgraduate work at St. Mary's Hospital, London, Cambridge University, the University of Vienna, the Academy of Medicine, Dusseldorf, Germany, the University of Paris and the University of Berlin. In the first World War he was an honorary Lieutenant in the Harvard University Surgical Unit with the British Expeditionary Forces in 1916; Captain, Royal Army Medical Corps, and Major, Medical Corps, U. S. Army in 1917; Chief Medical Examiner and Tuberculosis Specialist, Camp Lewis, 1917–1919; Chief of Medical Staff at Fitzsimons General Hospital, Denver, 1919–1920; and since then Lieutenant-Colonel, Medical Reserve Corps. His affiliations with medical societies, both national and international, are too numerous to mention except for a few—his Fellowship in the American College of Surgeons, the American College of Physicians; his past-presidency (1939) of the American College of Chest Physicians, and Presidency of the National Tuberculosis Association. His time was largely given in later years, aside from his large private practice, to the University of Oregon Medical School, on whose faculty he had served since 1903, to his post as Chief Surgeon of the University State Tuberculosis Hospital in Portland, and to his editorship of the publication *Diseases of the Chest.*

As a physician, Doctor Ralph never spared for himself a moment to which he thought his patients were entitled. They were not technical problems to him—but whole human beings, and he was passionately devoted to the cause of helping each one of them. Few doctors have had a greater following of devoted patients than he, although he was sharp in the face of weakness or dishonesty and uncompromising in his recommendations for medical care. No consideration ever transcended that of his patients' interests.

As an innovator, Doctor Matson's work in intrapleural pneumonolysis is one of the milestones in collapse therapy, and is internationally recognized. His instruments are known and widely used by thoracic surgeons everywhere, and many have come from all over the world to learn his matchless technique in the severing

of pleural adhesions. He was, of course, one of the earliest advocates of the forms of collapse therapy now so generally accepted, and none could even hazard an estimate as to the number of cases of lung disease which have benefited by his pioneering action, his firm and sure convictions, his tireless operating and scientific writing in this relatively new field. He helped immeasurably to build a strong sound base to a specialty that is offering a reprieve to thousands who would otherwise be eliminated by tuberculosis or other chest diseases.

Ralph C. Matson
1880–1943

As a teacher, Doctor Ralph's vivid quality was undiminished. Many men of action, or of research, are famously poor teachers. They can work but they cannot convey; they can recite facts, but not create inspiration. Around *him* enthusiasm was like a contagion. No one who ever sat with him in conference will ever forget the stimulating quality of his electric personality. The weekly staff meetings, at the University State Hospital, thrived with virulent expression of divergent views under his broad guidance. He had no patience with ineptitude, with carelessness or neglectfulness. Yet he showed endless patience with the

willing and eager student. His understanding of youth and his tolerance never waned, qualities which, with his debonair appearance, made him seem ageless.

As a man, Doctor Matson lived life fully and well. He filled each moment to the hilt—working with great earnestness, or playing with great zest, giving his buoyant enthusiasm to surgery or to polo—somehow achieving a constant pace that seemed to include no moments for sheer rest. His prankishness was well known to his friends, and the merriment of his eyes and his laughter were an overflow of his spirits that would have reached the humor of the most prosaic.

On October 26, 1945, Ralph C. Matson passed away at the Portland Open Air Sanatorium, the hospital in which much of his original work had been accomplished. Although his struggle with bronchial asthma had been long and discouraging, it is almost impossible to realize that his life is over. He seemed to have a great and inexhaustible fund of youth. The energy with which he lived and worked seems still to be in motion. Had he spared himself a little, he might have lived a few years longer, but then he would not have been *Ralph Matson*. One cannot mourn him without also feeling thankful that life was so abundant in this generous, brilliant and creative man. He will long continue to exist in his achievements and in the memory of those who knew him.

William S. Conklin

A DEPOT FOR STANDARD CULTURES OF TUBERCLE BACILLI

Report of the Committee on Standard Cultures of the Medical Research Committee of the National Tuberculosis Association

Dr. Leroy U. Gardner, *Chairman*

Dr. William H. Feldman
Dr. Max B. Lurie
Dr. M. I. Smith
Mr. William Steenken, Jr.
Dr. William Charles White
Dr. H. Stuart Willis

The Committee on Medical Research of the National Tuberculosis Association has agreed that the time has come to encourage the use of strains of tubercle bacilli whose origin, type and virulence are known and can, within limits, be guaranteed. The need for standards is particularly obvious in some of the reports of animal or other methods of assay of compounds proposed for the treatment of tuberculosis, in which evidence of full virulence of the infecting organisms is lacking or at least questionable. Moreover, it is now apparent that possible influences of virulence were not given due consideration in much of the chemical research upon the tubercle bacillus which has been sponsored by the Committee. Accordingly a Subcommittee was appointed to investigate the possibility of establishing a depot, supported by the National Association, for the maintenance of a limited number of standard cultures of tubercle bacilli whose virulence could be assured by controlled methods of cultivation and frequent animal tests. If this were feasible it was proposed to distribute without cost, to any qualified investigator, transplants of such cultures together with information on the history of the strain and data on the dosage required to produce particular effects. The only stipulation to the recipient would be the requirement that he mention in every report the fact that he had used one of these standard cultures.

The members of the Subcommittee, whose names are carried with this report, have met and decided to assume responsibility for this activity. A Depot is to be established at the Clinical and Research Laboratory in Trudeau Sanatorium under the immediate supervision of its bacteriologist, Mr. William Steenken, Jr.

It was agreed that at the outset the Depot should maintain the following strains of tubercle bacilli whose history and characteristics are widely known:

1: The Attenuated Human Strain, R1, using only its more virulent rough variant (Rv) (For vaccination experiments in animals.)
2: The Moderately Virulent Human Strain, H37.
  (a) Its more virulent rough variant, Rv.
  (b) Its avirulent rough variant, Ra.
3: The Virulent Bovine Strain, "Ravenel." (Virulent rough variant, Rv.)
4: The Virulent Avian "Strain 30," Phipps Institute. (Virulent smooth variant Sv.)
5: A Fully Virulent Human "Gary Strain," Maybury Sanatorium. (Virulent rough variant, Rv.)

The last culture was selected from a number of possibilities because it had been used without appreciable loss of virulence for a period of seventeen years and the effects of dosage had been established by long experience.

It was agreed that certain other strains like D.T., originating in the Hygienic Laboratory, from which the Standard Tuberculin, PPD, had been made, should be investigated and their present characteristics established.

The low virulent R1 strain and the avirulent dissociant of H37 are also included as they are good immunizing agents in guinea pigs.

Originally the Committee intended to include the attenuated strain, BCG, to be supplied with instruction that transplants were to be used only for animal experimentation. Subsequent reflection indicated that this proviso could not be enforced. It was, therefore, decided to eliminate this strain since the Depot will not have facilities to maintain the essential safeguards proposed after the Lübeck disaster.

The Committee accepts the following nomenclature for dissociants of *M. tuberculosis:*

Ra to designate avirulent organisms of rough colonies.
Rv to designate virulent organisms of rough colonies.
Sv to designate virulent organisms of smooth colonies.

Transplants of these cultures are now in the hands of our bacteriologist who will make a thorough study of each of them to determine their present condition, possible partial dissociation and virulence for appropriate animal host.

When pure line strains have been obtained from each they will be maintained on a standard medium. Animal inoculations will establish the dosage necessary to produce various kinds of disease and the probable duration of life.

Routine tests of virulence will be made at least once a year but, in addition, the Depot will receive frequent reports from the respective laboratories of the Committeemen who are using these cultures in routine experiments. The Committee will also collect and tabulate data from all publications by others who may use these strains. By these means a constant check upon virulence and purity of the strains should be possible.

Investigators desiring transplants of such strains should apply to: The National Tuberculosis Association Standard Culture Depot, Attention: Mr. William Steenken, Jr., Trudeau, New York.

Within three weeks they will receive, free of charge, a fresh transplant of the type of organism desired with an outline of its history, its current virulence for the common laboratory animal and the dosage required to produce various effects.

Recipients will be expected to indicate in all publications that they have worked with one of the standard type cultures, the date of its receipt from the Depot and if it was subsequently transplanted in their own laboratories, the type of medium employed and the number of subculture generations since its receipt.

For the information of prospective applicants, the Committee has agreed upon the following procedures which will be adopted as standard in the Depot. If subsequent experience indicates a need for changes, these will be indicated in

bulletins published by the Committee in the AMERICAN REVIEW OF TUBERCULOSIS and in the BULLETIN of the National Tuberculosis Association.

Standard culture medium: Until further notice all cultures will be maintained and dispensed upon Proskauer and Beck's fluid medium. Experiments with certain solid media will be carried on but at the present time it is believed that many such media tend to favor loss of virulence.

Transplant period: Every three weeks.

Frequency of formal virulence tests: One a year, but see above.

Animal hosts: Guinea pigs and rabbits.

Minimal number of animals for each virulence test: 5.

Weight of such animals: Guinea pigs, not less than 400 grams.
Rabbits, not less than 2 kilograms.

Type of inoculations: Guinea pigs, subcutaneous.
Rabbits, intravenous.

Preparation of suspensions: Growth from fluid medium is triturated in an agate mortar with a minimum amount of physiological salt solution until a homogenous paste is formed. This is taken up in about 10 ml. of saline and centrifuged at low speed for about two minutes to remove gross clumps of organisms.

To standardize the resultant suspension, an aliquot portion of the filtrate is removed to a watch glass, evaporated over a water bath and dried to constant weight. With allowance for the salt content, the weight of bacilli per ml. in the remainder of the suspending fluid can then be calculated. This method is more accurate than the common practice of partially drying the organisms by pressure between layers of filter paper.

Dosage:

Dry weight of organism in an aliquot portion of suspensions.

For guinea pigs, subcutaneous, 0.001 mg. human and bovine virulent and low virulent strains.

For rabbits, intravenous, 0.01 mg. bovine and avian strains.

Time limit of virulence tests:

Guinea pigs, all survivors of virulent infections to be killed fifty-six days after infection.

Rabbits, all survivors of bovine inoculations to be killed ninety days after infection.

Rabbits, all survivors of avian inoculations to be killed twenty-eight days after infection.

Severity of disease indicative of full virulence:

(a) Guinea pigs—Extensive *gross* tuberculosis of spleen and lymph nodes with or without other visceral involvement.

(b) Rabbits, bovine infection—Extensive *gross* tuberculosis of the lungs, with or without involvement of the kidneys and other viscera.

(c) Rabbits, avian infection—Either early death from Yersin form of tuberculosis with hypertrophy of liver and spleen and great numbers of bacilli in smears or later deaths with

gross miliary lesions throughout the spleen and smaller numbers of pin-point tubercles in the lungs.

Severity of disease after injection of low virulent organisms:

(a) Guinea pigs (R1)—Proliferative, caseous involvement of regional lymph nodes with occasional localized tubercles in spleen.

(H37 Ra) Local lymph node lesion only, resolving in five to six months.

NOTICE

American Public Health Association

The Executive Board of the American Public Health Association announces the 74th Annual Meeting of the Association to be held in Cleveland, Ohio, the week of November 11, 1946.

This will be the first full-scale convention of this professional society of public health workers since 1942. In 1943 and 1944, streamlined wartime congresses on public health were held and in 1945, for the first time in its history, the organization held no Annual Meeting.

An attendance of 4,000 is anticipated, representing every state in the United States, Canada, South America and many countries outside this hemisphere.

Dr. Harold J. Knapp, Cleveland's Health Commissioner, has been appointed the Chairman of the Local Committee.

RESULTS OF BCG IMMUNIZATION IN NEW YORK CITY[1,2]

MILTON I. LEVINE AND MARGARET F. SACKETT

Since 1922, when Calmette suggested vaccination of human beings against tuberculosis by means of BCG vaccine, more than 2,000,000 children have been vaccinated throughout the world. The majority of these vaccinations have been performed in various countries of Europe, Africa and Asia, although they have been used to a lesser degree in North and South America.

Most reports have been optimistic, but the vast majority of these studies have been inadequately controlled. The very nature of the problem makes selection of controls a difficult one because of the many factors which may influence the incubation and the clinical course of tuberculosis. Ideal control would call for consideration of the following variables:

Environmental Conditions
1. Intelligence and coöperation of parents.
2. Difference in localities
3. Differences in time during which controls and vaccinated cases were studied.

Exposure Conditions
1. Frequency of exposure.
2. Amount of sputum expectorated.
3. Number of microörganisms in sputum.
4. Intensity of exposure.

Other Factors
1. Age at first exposure.
2. Racial differences.
3. Reliable diagnosis at death.
4. Identical follow-up of control and vaccinated cases.
5. Maintaining contact with all cases.
6. Freedom from exposure for similar periods in both groups, if separation is advisable for either group.
7. Study of adequate numbers of subjects to minimize results of chance distribution.

In no study thus far reported have all these factors been considered and adequately controlled. In some studies the mortality rate from tuberculosis of the general population was compared with the vaccinated group; in others a different age group served as a control; in some the tuberculosis mortality of vaccinated children was compared with the tuberculosis mortality of previous years; in other studies the controls comprised cases where vaccination was refused; in still others the control group was less carefully followed than the vaccinated group; in one study, only the vaccinated cases were temporarily separated from the tuberculous source. In many observations controls were entirely omitted. In brief, then, conclusions stemming from most of the previous work are open to criticism. Table 1 includes most of the reported studies with the manner of control selection.

[1] From the New York Hospital and the Department of Pediatrics, Cornell University Medical College, and the Bureau of Laboratories, New York City Department of Health.
[2] Aided by a grant from Mead Johnson & Company, Evansville, Indiana.

TABLE 1

Reported results of BCG studies with method of control selection

COUNTRY	CITY	AUTHOR	CHILDREN VACCINATED	TUBERCULOSIS MORTALITY	CONTROLS	TUBERCULOSIS MORTALITY	METHOD OF CONTROL SELECTION
Argentina	Cordoba 1938–1941	Chattas (20)	20	1 death 5.0%	20	2 deaths 10.0%	Method of selection not given.
Brazil	Sao Paulo 1926–1931	Ferreira (1)	619	0.16%	159	3.1%	Controls were children "not vaccinated because they gave a positive reaction to tuberculin."
Canada	Montreal 1926–1938	Baudoin (2)	20,000 vaccinated; 793 cases in contact with tuberculosis	8 deaths 1.13%	1,200	23 deaths 1.92%	"Controls were children living under similar condition as vaccinated cases."
Cuba	Havana 1928–1932	Jaime, Ferrer (1)	84 vaccinated; 32 with tuberculosis contact	1.3%	None	—	—
Czecho-Slovakia	Prague 1927–1931	Danicek (1)	2334 newborn vaccinated; 363 followed, of which 72 had tuberculosis contact	0	None	—	—
Denmark	Copenhagen 1927–1932	Jensen (1)	56 newborn infants; 19 with tuberculosis contact	0	General infant popula.	4.9%	Few followed vaccinated cases compared with general infant population
Greece	Athens 1925–1931	Lompadarios (1)	2,920	0.2%	None	—	—
Ireland	St. Ultans 1937–1938	Price (10)	5 (one of which was lost)	0	None	—	—
Italy	Turin 1929–1930	Allaria, Borsarelli (1)	303; 53 tuberculosis contacts	0	None	—	—
Italy	Fiume 1929–1931	Persich (1)	535 newborn	0	None	—	—
Italy	Trieste	Isreali (1)	92 newborn, all tuberculosis contacts	1.0%	None	—	—
Jugoslavia	Belgrado 1928–1931	Kostic-Yoksik (1)	1062 newborn; 225 followed; only 55 with tuberculosis contact	0	None	—	—
Netherlands	Amsterdam 1926–1932	Aldershoff, Van den Berg (1)	408	2.1%	Number not given	18.9%	Method of selection not given.
Poland	Poson 1928–1938	Zeyland and Pinsecka-Zeyland (4)	12,135 vaccinated; 438 exposed to tuberculosis	4 deaths 0.91%	76	8 deaths 10.5%	Controls were cases where vaccination was refused.
Poland	Warsaw 1927–1931	Wierzbowska (1)	6,958	0	Infants in Warsaw	3.7%	General population compared with followed vaccinated group.
Poland	Wilna 1928–1930	Baginski (16)	600; 144 followed; 32% exposed to tuberculosis	0.7%	Infants in Wilna	2.9%	General population compared with followed vaccinated group.
Roumania	Bucharest 1928–1933	Cantacusène Nasta, Veber (9)	45,000 vaccinated; 800 exposed to tuberculous families	1st yr.—1.8% 2nd yr.—0.46% 3rd yr. 0.11%	None	—	—

Roumania	Asuga	Cantacusène, Nasta, Veber (9)	241 vaccinated; 16 from tuberculous families	1 death 0.2%	None	—	—
Roumania	Missinan	Cantacusène, Nasta, Veber (9)	7,203 vaccinated; 511 from tuberculous families	0.4%	None	—	—
Roumania	Cetatea Alba 1931–1933	Cantacusène, Nasta, Veber (9)	265 vaccinated; 128 from tuberculous families	0	Number not given	3 deaths	Method of control selection not given.
Roumania	Iassy 1928–1933	Cantacusène Nasta, Veber (9)	1,752 vaccinated	0	None	—	—
Roumania	Targoviste 1926–1933	Cantacusène, Nasta, Veber (9)	1,071 vaccinated; 120 from tuberculous families	0	None	—	—
Roumania	Caracel 1927–1933	Cantacusène Nasta, Veber (9)	1,512 vaccinated; 65 from tuberculous families	1 death	Number not given	7 deaths	Method of control selection not given.
Roumania	District Falciu 1931	Cantacusène Nasta, Veber (9)	165 vaccinated; 18 from tuberculous families	0	None	—	—
Roumania	District of Ilfoo 1929–1933	Cantacusène Nasta, Veber (9)	10,794; 609 from tuberculous families	5 deaths 0.82%	None	—	—
Roumania	Barlad 1928–1933	Cantacusène Nasta, Veber (9)	1,637; 165 from tuberculous families	0	None	—	—
Roumania	Dragasani 1928–1933	Cantacusène, Nasta, Veber (9)	863; 35 from tuberculous families	0	None	—	—
Roumania	Crajowa 1927–1933	Cantacusène, Nasta, Veber (9)	4,364; 38 from tuberculous families	0	None	—	—
Roumania	Resita 1928–1932	Cantacusène, Nasta, Veber (9)	671 vaccinated; 68 from tuberculous families	0	None	—	—
Roumania	Braila 1928–1933	Cantacusène, Nasta, Veber (9)	2,739; 1,002 followed	0	511	0.78%	Method of control selection not given.
Roumania	58 towns and villages	Cantacusène, Nasta, Veber (9)	100,000 newborn	0 to 3.8%	Infants in Bucharest	25%	Controls from heavily populated area. Vaccinated cases from 58 towns and villages.
Russia	Leningrad 1928–1936	Medowskow (5)	3,629; 905 exposed to active tuberculosis	0.52%	None	—	Compares own vaccinated cases with controls from literature.
Russia	Kazan	Poklitonova (11)	122 exposed cases	Birth to 1 yr., 6.3%; 1 to 2 yrs., no mortality	158 exposed cases	Birth to 1 yr., 5.8%; 1 to 2 yrs., 10.3%	Not stated.
Russia	Moscow	Poklitonova (11)	45	4.8%	42	16.3%	Not stated.
Russia	Leningrad	Poklitonova (11)	552	2.9%	None	—	—
Russia	Konochinkov	Poklitonova (11)	560	Birth to 1 yr., 2.9%; over 1 yr., 0.6%	227	Birth to 1 yr., 8.8%; over 1 yr., 1.9%	Not stated.
Russia	Kharkoff	Iakhnis Tzekanovitzer (1)	2,226 newborn; 187 exposed to tuberculosis	Birth to 1 yr., 3.0%; 1 to 2 yrs., 2.8%; 2 to 3 yrs., 0.9%	118 newborn, exposed to tuberculosis	Birth to 1 yr., 16%; 1 to 2 yrs., 13%; 2 to 3 yrs., 11%	Not stated.
Russia		Iakhnis (15)	20	0	20	0	Vaccinated one of twins in tuberculous families. Held other as control.

TABLE 1—*Continued*

COUNTRY	CITY	AUTHOR	CHILDREN VACCINATED	TUBERCULOSIS MORTALITY	CONTROLS	TUBERCULOSIS MORTALITY	METHOD OF CONTROL SELECTION
Spain	Barcelona	Saye (1)	8,200	Birth to 1 yr., 3.78%; 1 to 2 yrs., 1.24%; 2 to 3 yrs., 0.33%; over 3 yrs., 0	40	Birth to 1 yr., 14.20%; 1 to 2 yrs., 0.22%; 2 to 3 yrs., 4.0%; 3 to 4 yrs., 3.42%	Controls from families with open tuberculosis where first and second child died of tuberculosis.
Sweden	Gothenberg 1927–1931	Wallgren (5)	230 exposed cases	0	General infant popula.	1922–26 0.34%; 1927–31 0.17%	Controls are infants of general population, whereas vaccinated cases are separated from source of infection 3 months after vaccination.
Sweden	Norbotten	Naeslund (3)	13,103 newborn	1.5%	34,845	6.3%	Controls are nonvaccinated children of general population.
Sweden	Gothenberg 1927–1939	Anderson and Belfrage (0)	1,069; 393 exposed to tuberculosis	0	Few cases who refused vaccination	5 deaths	Controls were few cases where vaccinations were refused.
United States	Nashville 1928–1931	Overton (1)	204 newborn; 4,070 older children; 1,500 school children	1 death of ? meningitis	None	—	—
United States	Baltimore 1927–1934	Aronson and Dannenberg (7)	41 exposed to positive sputum	2.4%	84 exposed to positive sputum	11.9%	
United States	Chicago 1936–1943	Rosenthal, Blahd, Leslie (21)	Noncontact 1,204 (184 followed 5 years or more)	1 death 0.09%	Noncontact 1,213 (194 followed 5 years or more)	4 deaths 0.33%	Controls were "too old for vaccination when first observed in clinic." "With the onset of the control group, cases were strictly alternated according to relationship of source, degree of involvement, and positive or negative sputum." Of contact cases, 58 vaccinated children were followed 2 years or more, whereas only 14 controls were followed 2 years or more. Age and race distribution of cases not given.
			Contact 98 (58 followed 2 years or more)	0	Contact 63 (14 followed 2 years or more)	3 deaths 4.70%	
United States	Indians of Arizona, Wyoming, South Dakota, North Dakota, Alaska, 1936–1938	Townsend, Aronson, Saylor, Parr (25)	1,565 persons, age 1 to 19 years	3 deaths 0.10%	1,450, ages 1 to 19 years	11 deaths 0.75%	Controls were "same age and sex, living in same area under precisely same conditions." Ages and localities of persons who died not given. Authors' note: "No definite conclusions should be drawn at this time as to the protective value of vaccine."
Uruguay	Montivideo 1925–1931	Saenz (1)	14,140 newborn orally vaccinated; 582 exposed to tuberculosis	1.03%	None	—	—

Other authors who have published favorable studies on BCG inoculation, but who based their findings on comparisons in general mortality rather than tuberculosis mortality of vaccinated children and controls, are: Gonsala (Spain) (1); Landa (Spain) (1); Mallard (Gold Coast) (1); Kenn (Gold Coast) (1); Dvorschak, Schlachter, Kuksar (Hungary) (1); Blanshard (Dakar) (1); Serqut, Ducros, Rougebief (Algeria) (1); Girard (Madagascar) (1); Danicek (Czecho-Slovakia) (17); Prokopowics Wierabowska (Poland) (19); Lotty (France) (1); Brelion (France) (14); Guérin (France) (12); Weill-Hallé (France) (13); Paraf and Boissonet (France) (8).

In December, 1926, a study of the efficacy of the BCG vaccine was undertaken by the Bureau of Laboratories of the New York City Department of Heath, under the direction of the late Dr. William Hallock Park (23). After numerous animal experiments had proved the vaccine to be harmless the vaccination of children was begun (24).

Up to January 1, 1944, 2,084 children of tuberculous families had been followed, of which 1,011 were vaccinated and 1,073 held as controls. The children were followed for varying periods according to their date of birth. Some were followed for varying periods according to their date of birth. Some were followed as long as sixteen years, while the children last taken up for study have been followed at least five years. The present paper confines itself to the first five years of life not only because all children were followed for at least that period of time, but because, with only one exception, all tuberculous deaths occurred in that age group.

METHOD OF STUDY

All children were referred from various tuberculosis clinics and hospitals in New York City. They were all from tuberculous families and, with rare exceptions, were placed under observation before they were 12 months of age, many of them during the first four weeks of life. No children were accepted for study after one month of age unless tuberculin tests up to 1.0 mg., roentgenograms and physical examinations were negative.

In the first two years of study the vaccine was given orally during the first ten days of life. By this method approximately 50 per cent developed positive tuberculin reactions. Thereafter the parenteral method of vaccination was used and it resulted in approximately 85 per cent positive tuberculin tests.

An attempt was made to follow the vaccinated and control cases with equal care. They were visited every month by staff nurses, and every three to six months by staff pediatricians. Tuberculin tests and roentgenograms were taken at fairly regular intervals.

Intracutaneous tests were performed by one of the staff pediatricians with freshly diluted Old Tuberculin furnished by the Department of Health of New York City. The routine dose of tuberculin was 0.1 mg., the dose being raised to as high as 10.0 mg. in certain instances. The reactions were read and measured at the end of forty-eight hours by specially trained nurses.

At the start of the work an attempt was made to control the study by dividing

accepted children into two equal groups: those to be vaccinated and those serving as controls. Under this system a physician was assigned to a number of cases and was told to vaccinate half of the group. Subsequent experience has shown that by this method of selection the tendency was to inoculate the children of the more intelligent and coöperative parents and to keep the children of the non-coöperative parents as controls. This was probably of considerable error since the coöperative parent will not only keep more careful precautions, but will usually bring the child more regularly to the clinic for instruction as to child care and feeding.

TABLE 2

Results January 1, 1933—Prior to institution of alternate selection

	CASES	TUBERCULOSIS DEATHS	
		Number	Per cent
Vaccinated	445	3	0.68
Controls	545	18	3.38

TABLE 3

Comparative results before and after alternate selection

	CASES	TUBERCULOSIS DEATHS	
		Number	Per cent
Total Cases			
BCG vaccinated	1,011	11	1.08
Controls	1,073	26	2.42
Cases 12/15/26–1/1/33 (before alternate selection)			
BCG vaccinated	445	3	0.68
Controls	545	18	3.38
Cases 1/1/33–1/1/44 (after alternate selection)			
BCG vaccinated	566	8	1.41
Controls	528	8	1.51

This arbitrary division of cases for vaccination and controls was followed from 1927 to January 1, 1933. In all, 990 children were studied, 445 of whom were vaccinated. The results are shown in table 2.

The procedure of selection was changed on January 1, 1933, so that alternate children were routinely vaccinated, the remainder serving as controls. The selection was made at headquarters as soon as the names were received and before they were assigned to staff pediatricians. If a family appeared very uncoöperative it was not taken up for study. Certain other cases were dropped if within a short period of time the tuberculous member of the family died in the hospital without ever having exposed the child. In some instances the tuberculin test on the first visit proved positive, a result which also caused the elimination of the

child from the study. These conditions, then, were responsible for the difference in number of controls and vaccinated children.

A total of 1,094 children were studied; 566 vaccinated (all intracutaneously with 0.15 mg. BCG) and 528 controls. The results of this period of alternate selection as compared with the previous period are shown in table 3. In the first period the tuberculosis mortality of the controls was over four times that of the vaccinated group; in the second period, the figures were essentially similar.

DISCUSSION

In order to determine the effect of alternate selection on *parental coöperation*, the first year clinic visits were tabulated for the two groups before and after January 1, 1933, since attendance at the clinic was advised but not forced (table 4).

Another criterion of the degree of coöperation was the type of care the child was given as judged by the visiting nurses regardless of attendance in BCG clinics,

TABLE 4

Average number of clinic visits during first year

	VACCINATED CASES	CONTROLS
Before 1/1/33	3.6	1.7
After 1/1/33	2.8	2.4

TABLE 5

Good coöperation of parents (per cent) as judged by visiting nurses

	VACCINATED CASES	CONTROLS
Before 1/1/33	43.1	23.8
After 1/1/33	39.7	33.5

since a few of the children attended other clinics. The opinion of these nurses is shown in table 5.

These figures as well as the number of clinic visits in the first year would tend to show that the coöperation of the vaccinated group was appreciably greater than that of the control group prior to the period of alternate selection, with considerably closer approximation in this latter period.

As already stated, other variables besides coöperation might have caused this shift in mortality rates. These factors required appraisement before acceptance of the final figures:

(a) *Differences in exposure to positive sputum between the two groups before and after January 1, 1933:* Table 6 shows that changes in exposure were so slight that their influence on the comparative results is probably negligible. It is interesting to note how similar was the degree of exposure in the two groups after the institution of alternate selection.

(b) *Differences in racial distribution of vaccinated and control cases in the two periods:* This factor is of potential importance in view of the high tuberculosis mortality among Negroes. Here again, the evidence is of a negative nature (table 7). There is a proportional increase in the percentage of Negro infants in both vaccinated and control groups after January 1, 1933. It may be noted that there was a greater increase in vaccinated Porto-Rican infants over controls after this same date, but deaths from tuberculosis among this racial group diminished rather than increased without relation to vaccination after alternation of cases was instituted. The change in mortality among controls in the two periods is found in the group of white infants whose percentage of tuberculosis dropped from 2.2 before January 1, 1933 to 0.28 per cent after.

TABLE 6

Exposure

	TOTAL CASES	+ SPUTUM EXPOSURE		− SPUTUM EXPOSURE		NO EXPOSURE	
		Number	Per cent	Number	Per cent	Number	Per cent
Cases 12/15/26–1/1/33 (before alternate selection)							
BCG vaccinated	445	214	48.2	119	26.7	112	25.1
Controls	545	286	52.6	185	34.0	73	13.4
Cases 1/1/33–1/1/44 (after alternate selection)							
BCG vaccinated	566	298	52.6	233	41.1	35	6.3
Controls	528	276	52.2	225	42.6	27	5.1

TABLE 7

Racial distribution

	TOTAL CASES	WHITE		NEGRO		PORTO RICAN	
		Number	Per cent	Number	Per cent	Number	Per cent
Cases 12/15/26–1/1/33 (before alternate selection)							
BCG vaccinated	445	335	75.0	63	14.0	45	11.0
Controls	545	409	75.0	66	12.1	70	12.8
Cases 1/1/33–1/1/44 (after alternate selection)							
BCG vaccinated	566	344	60.8	108	19.0	113	20.0
Controls	528	352	66.6	88	16.6	86	16.2

(c) *Differences in economic conditions of the two groups before and after January 1, 1933:* This also does not appear to be of importance (table 8). The increase in poor economic condition of families taken up after 1933 coincides with the period of national depression. The figures show an increase in poor economic

conditions of both vaccinated and control cases after January 1, 1933, although more pronounced among those vaccinated.

However, the tuberculosis mortality did not vary directly with the earning conditions, as evidenced by a tabulation of total cases, 1926–1938 (table 9).

(d) *Could the difference in tuberculosis mortality between the periods before and after January 1, 1933 be due to a change in the number of cases lost?* In the latter

TABLE 8

Economic conditions

	TOTAL CASES	GOOD EARNING CONDITIONS		FAIR EARNING CONDITIONS		POOR EARNING CONDITIONS	
		Number	Per cent	Number	Per cent	Number	Per cent
Cases 12/15/26–1/1/33 (before alternate selection)							
BCG vaccinated	438	139	31.8	116	26.4	183	41.4
Controls	545	138	25.3	151	27.7	256	47.0
Cases 1/1/33–1/1/44 (after alternate selection)							
BCG vaccinated	564	93	16.5	125	22.1	346	61.3
Controls	528	79	15.0	159	30.1	290	54.9

TABLE 9

Relation of earnings to tuberculosis mortality

EARNING CONDITION	TOTAL CASES	TUBERCULOSIS NUMBER	DEATHS PER CENT
Vaccinated cases			
Good	233	3	1.29
Fair	241	1	0.41
Poor	528	6	1.13
Controls			
Good	222	2	0.90
Fair	304	10	3.25
Poor	547	9	1.64

Poor = 0 to $4.00 per week per person.
Fair = $4.00 to $8.00 per week per person.
Good = $8.00 and over per week per person.

period,[3] the number of lost cases among both controls and vaccinated cases was considerably smaller than in the previous years. There was no evience to show that this factor had any bearing on the shift in mortality (table 10).

(e) *Variations in the number of autopsies* performed in the two periods might be implicated as a cause for the variance in tuberculosis mortality figures. A

[3] During this period, of the 78 cases lost, 52 moved from New York to other localities and 26 cases moved and could not be traced. An investigation by the Bureau of Vital Statistics of New York City failed to reveal any of the lost cases among the recorded deaths.

previous paper (22) has emphasized the importance of postmortem examinations in arriving at an accurate diagnosis. Autopsy records are shown in table 11. The figures show how much greater was the opportunity for accurate diagnosis at death in the group taken up after January 1, 1933. There is no evidence that this increase in autopsy examinations had any bearing on the shift in tuberculosis mortality.

(f) Since the tuberculosis mortality of the vaccinated cases increased after January 1, 1933, the question also arises as to whether there was any *loss in the activity of the BCG vaccine.* A history of the BCG vaccine used in the New York Study is as follows:

TABLE 10

Lost cases

	TOTAL CASES	LOST	
		Number	Per cent
Before 1/1/33			
Vaccinated	445	100	22.47
Controls	545	127	23.30
After 1/1/33			
Vaccinated	566	29	5.12
Controls	528	49	9.28

TABLE 11

Postmortem examinations before and after January 1, 1933

	TOTAL CASES	TOTAL DEATHS	AUTOPSIES	
			Number	Per cent
Before 1/1/33				
Vaccinated	445	36	17	47.1
Controls	545	46	18	39.1
After 1/1/33				
Vaccinated	566	22	17	77.2
Controls	528	33	20	60.6

The original BCG culture was obtained by Dr. William H. Park from Calmette in 1926 and brought to the United States. Strains of this culture were sent to the Mt. McGregor Sanatorium and to the Phipps Institute. This culture was used in the preparation of the vaccine until late in 1932 when it became contaminated by molds. Pure cultures were at last obtained by the antiformin method and plated on media containing aniline dyes (Loewenstein's and modified Petroff medium). Meanwhile, subcultures were obtained from the Phipps Institute. These cultures were used alternately for vaccine for a period of one year. After this time both cultures were used without selection. Virulence tests were made

at three-month intervals but no tests were made for potency. However, it is to be noted that the percentage of positive tuberculin reactions resulting from the BCG inoculations did not decrease after January 1, 1933, there being 87.1 per cent before as against 87.6 per cent after that date. It seems logical, therefore, to accept the group of cases obtained through alternate selection as a fair basis for study of the efficacy of the BCG inoculation against tuberculosis.

The children taken up after January 1, 1933 have further qualifications, besides the close proportion in relation to exposure, which make them favorable for study. All were taken up when they were under one year of age, they were all inoculated intracutaneously and received a standard dosage of 0.15 mg. BCG vaccine.

Before these results may be accepted as demonstrating the inadequacy of BCG vaccine as a prophylactic measure against tuberculosis, several further possible influencing factors must be considered.

In the first place, since it takes six to eight weeks for a tuberculin reaction to become positive after infection with the tubercle bacillus, is it not possible that certain of the children who died had tubercle bacilli already in their bodies but were still in a pre-allergic phase when tuberculin tested before receiving the BCG vaccine? And could it be possible that some of these vaccinated cases were exposed massively to positive sputum immediately after vaccination and before the vaccine had an opportunity to exert its effect? A summary of all tuberculosis deaths among BCG vaccinated cases (shown in table 12) reveals the following:

(1) All 11 cases were exposed to positive sputum.

(2) All cases except one (N. M.) were definitely exposed to virulent human tubercle bacilli in their homes within five weeks before vaccination.

(3) In 9 of the 11 deaths, autopsies were performed verifying the diagnosis, and in 8 of the cases where bacteriological studies were performed the organism obtained was a human strain of tubercle bacillus.

This latter factor, bacteriological examination, is of extreme importance in the case of vaccinated children since it is conceivable that one might attribute the deaths to BCG unless bacteriological examinations proved otherwise, Thus far, no authentic cases of tuberculosis deaths due to the BCG organism have been reported in the literature.

The question naturally arises as to whether the deaths among the BCG vaccinated cases were due to a tuberculous infection previous to vaccination, or whether the vaccination was an inadequate protection against a subsequent infection. This is difficult to answer.

This question, however, brings up the problem as to what results would be obtained if cases were separated before vaccination to prevent the inoculation of a child in the pre-allergic phase, and if the same cases were separated for a sufficiently long period after inoculation to permit the vaccine to take effect. For a more accurate answer it would be necessary to separate all subjects for a minimum of three months before and three months after vaccination. We have found it a dangerous policy to institutionalize children during the first three months of life, since they so often contract infections in the hospital or home to which they

TABLE 12

Vaccinated cases who died of tuberculosis

CASES	EXPOSURE	SPUTUM OF TUBERCULOSIS CASE	AGE AT VACCINATION	AGE AT DEATH	AUTOPSY	BACTERIOLOGY
				months		
Parenterally vaccinated						
R. D.	Birth to 3 months	Positive	3¼ mos.	8	Tuberculosis	Human tubercle bacilli
J. W.	Birth to death	Positive	3 weeks	4½	Tuberculosis	Human tubercle bacilli
P. F.*	Birth to 5¼ months	Positive	1½ mos.	9¾	Tuberculosis	No bacteriology. Tissues placed in formaldehyde
J. K.	Birth to 1¼ months	Positive	1¼ mos.	3	Tuberculosis	Human tubercle bacilli
R. M.	Father with positive sputum, birth to 1 month. Mother with negative sputum, birth to death	Positive	1¾ mos.	13	Tuberculosis	Human tubercle bacilli
J. P.	Birth to 9 months	Positive	9¼ mos.	14¾	Tuberculosis	Human tubercle bacilli
C. B.	Birth to 1¾ months	Positive	3 mos.	16	Tuberculosis	Human tubercle bacilli
J. V.	Birth to death	Positive	1 week	25½	0	None
Orally vaccinated						
N. M.**	None known	Positive	1st week	3	0	None
M. R.***	Occasional exposure, birth to death	Positive	1st week	32	Tuberculosis	Human tubercle bacilli
L. L.	Birth to death	Positive	1st week	8	Tuberculosis	Human tubercle bacilli

* This case was autopsied and all specimens saved were placed in fixing solution. This prevented any bacteriological studies.

** This baby was born of a mother dying of an overwhelming tuberculous infection. The latter died shortly after giving birth. The child was vaccinated by mouth during the first week and died of tuberculosis at 3 months of age. No autopsy was performed. Diagnosis made on X-ray findings.

*** Died of bronchopneumonia following pertussis. X-ray suggestive of miliary tuberculosis. However, no tubercles were found in the lungs on autopsy. Bacteriological examination negative for tubercle bacilli in the lung tissue but positive in mediastinal lymph nodes. No tuberculosis in other parts of body.

are sent. As a matter of fact, it appears that many more babies, so separated, died during this period of nontuberculous causes than would have died of tuberculosis had they remained at home. Table 13 brings out clearly the danger of institutionalizing babies at such an early age.

However, in the course of our studies a certain number of exposed children chanced to be separated for three months before and three months after vaccination. It is to this group, then, that we must look for any trend that might give an indication of the value of the inoculation. One may for this particular study

TABLE 13

Study of the mortality of infants during the first three months of life

	INFANTS HOSPITALIZED DURING FIRST THREE MONTHS OF LIFE AS WELL-BABIES	INFANTS NOT HOSPITALIZED DURING FIRST THREE MONTHS OF LIFE
Total number	120	949
Number of nontuberculosis deaths in first three months	14 (11.6%)	9 (0.9%)
Cause of deaths gastrointestinal intoxication	10	5
Pneumonia	2	4
Foreign body in trachea	1	
Thymus (?)	1	

Note: Premature babies who died under one month of age are not included in the above figures.

TABLE 14

Exposed cases separated three months before and three months after being vaccinated or taken up

	NUMBER OF CASES	TUBERCULOSIS DEATHS	
		Number	Per cent
Vaccinated	91	1*	1.1
Controls	96	3**	3.1

* This child was born of a mother dying of tuberculosis; was never exposed; died at 3 months of age.

** One case with no known exposure died of tuberculosis at 15 months of age.

take all such cases followed since the onset of the BCG experiment in New York City, all cases segregated from tuberculous infection during the full six months' period. For comparison, one must include also all controls separated three months before and three months after the date they were admitted for study. The results are shown in table 14. It would appear from these figures that the inoculations with BCG might be of some protection if children were separated from the tuberculous environment for a sufficiently long period of time before and after vaccination. From a scientific viewpoint, in justice to BCG, its efficacy in preventing tuberculosis should be judged only from results of cases

definitely not infected with human tubercle bacilli before vaccination and not exposed after vaccination until allergy has developed from the BCG administration. However, from a public health standpoint its efficacy must be judged by its ability to reduce adequately the tuberculosis mortality of children vaccinated in their homes in the midst of a tuberculous environment.

It would appear, therefore, from these statistical results that as a public health measure the routine vaccination with BCG of children from tuberculous homes is probably of less advantage than removing the tuberculous case from the home.

SUMMARY

1. More than 2,000,000 children throughout the world have been vaccinated with BCG.

2. The published reports on the effectiveness of the vaccine as a prophylactic against tuberculosis have been predominantly optimistic. With few exceptions, these studies have been inadequately controlled.

3. Up to January 1, 1944, 2,084 children from "tuberculous homes" in New York City have been followed, of whom 1,011 were vaccinated and 1,073 held as controls.

4. A comparison is made of the tuberculosis mortality before and after alternate selection of cases.

5. Prior to the alternation of cases, the tuberculosis mortality of the controls was over four times that of the vaccinated group (3.38 as against 0.68 per cent). In the second period, following alternation, the figures for the two groups were essentially similar, the tuberculosis mortality of the vaccinated cases being 1.41 per cent as against 1.51 for the controls.

6. The possible effect of the following factors on the comparative results was assessed: parental coöperation, economic condition, racial distribution, exposure, lost cases and percentage of autopsies.

7. Routine separation of children for three months before and three months after BCG vaccination to eliminate the hazard of contiguous contamination with human tubercle bacilli was not found to be a feasible or safe procedure, although a small sample where such separation was possible (91 vaccinated and 96 control cases) indicated that the BCG inoculation might have protective value were such separation practical.

8. From a public health standpoint, however, the efficacy of BCG must be judged by its ability to reduce the tuberculosis mortality of children vaccinated in their homes in the midst of a tuberculous environment.

9. As a public health measure, therefore, the routine vaccination with BCG of children from tuberculous homes is less advantageous than removal of the tuberculous subject from the home.

SUMARIO

1. A más de 2,000,000 de niños en todo el mundo se les ha vacunado con BCG.

2. En los informes publicados acerca de la eficacia de esta vacuna como

profiláctico de la tuberculosis ha predominado el optimismo pero, con pocas excepciones, esos estudios han sido inadecuadamente fiscalizados.

3. Hasta el 1°. de enero de 1944 se ha observado a 2,084 niños procedentes de "hogares tuberculosos" en la ciudad de Nueva York, de los cuales, 1,011 fueron vacunados y 1,073 retenidos como testigos.

4. Compárase la mortalidad tuberculosa antes y después de la selección alternada de casos.

5. Antes de alternarse los casos, la mortalidad tuberculosa en los testigos era el cuádruple que en el grupo vacunado (3.38 comparado con 0.68%). En el segundo período, después de alternarse los casos, las cifras vinieron a ser idénticas en ambos grupos, representando la mortalidad tuberculosa 1.41% en los vacunados, comparada con 1.51% en los testigos.

6. Se justiprecia el posible efecto de los siguientes factores sobre el resultado comparativo: cooperación paternal, estado económico, distribución étnica, exposición, casos perdidos de vista y porcentaje de autopsias.

7. La separación sistemática de los niños durante tres meses antes y tres meses después de la vacunación con BCG para eliminar el riesgo de la contaminación contigua con los bacilos tuberculosos humanos, no resultó factible o segura, aunque en una pequeña muestra (91 casos vacunados y 96 testigos) en la que dicha separación resultó posible, indicó que la inoculación con BCG podría tener valor protector si resultara práctica.

8. Sin embargo, desde el punto de vista sanitario, hay que juzgar la eficacia de BCG por su capacidad para rebajar la mortalidad tuberculosa de los niños vacunados en sus hogares en un ambiente tuberculoso.

9. Por lo tanto, como medida sanitaria, la vacunación sistemática con BCG de los niños procedentes de hogares tuberculosos, resulta menos ventajosa que la separación de los tuberculosos del hogar.

BIBLIOGRAPHY

(1) Vaccination Préventative de la Tuberculose, Rapports et Documents, Institut Pasteur, Paris, 1932.
(2) Hopkins, J. W.: Am. Rev. Tuberc., 1941, *43*, 581.
(3) Naeslund, C.: Rev. de la tuberc., 5th Series, 1939, *5*, 710.
(4) Zeyland, I., and Piasecka-Zeyland, E.: Acta paediat. 1940, *27*, 393.
(5) Medovikov, P.: Probl. tuberc., 1937, *6*, 81.
(6) Anderson, H., and Belfrage, H.: Acta paediat., 1939, *26*, 1.
(7) Aronson, J., and Dannenberg, A.: Am. J. Dis. Child., 1935, *50*, 1117.
(8) Paraf and Boissonet: Presse méd., 1937, *45*, 1307.
(9) Cantacusène, Nasta and Veber: Arch. Roum. de path. expériment et de microbiol., 1933, *6*, 135.
(10) Price, D.: Irish J. M. Sc., July, 1942, p. 252.
(11) Poklitonova, P.: Rev. phtisiol. Thér. et Soc., 1934, *15*, 224.
(12) Guérin: Acad. méd. Paris, III, 1934, *3*, 773.
(13) Weill-Hallé, B.: Bull. Acad. de méd., Paris, 1931, *106*, 45.
(14) Brelion, P.: Bull. Acad. de méd., Paris, 1932, *108*, 1486.
(15) Iakhnis, B., Vopr. tuberk., 1931, *9*, 953.
(16) Baginski, S.: Gruzlica, 1931, *6*, 260.

(17) DANICEK: Presse méd., 1932, *42*, 1440.
(18) CALMETTE, A.: Proc. Roy. Soc. Med., 1931, *24*, 1481.
(19) PROKOPOWICS WIERABOWSKA: Rev. d'hyg., 1936, *58*, 531.
(20) CHATTAS, A.: La Vacunacion Antituberculosa cou el B.C.G., University Cordoba, Argentina, 1942.
(21) ROSENTHAL, BLAHD AND LESLIE: J. Pediat., 1945, *26*, 470.
(22) LEVINE, M. I., VOGEL, P., AND ROSENBERG, H. A.: Am. Rev. Tuberc., 1938, *38*, 632.
(23) KING, M. J., AND PARK, WM. H.: Am. J. Pub. Health, 1929, *19*, 179.
(24) KERESZTURI, C., AND PARK, WM. H.: Am. Rev. Tuberc., 1929, *20*, 297.
(25) TOWNSEND, J. G., ARONSON, J. D., SAYLOR, R., AND PARR, I.: Tr. Nat. Tuberc. A., 37th Annual Meeting, 1941, p. 66.

THE TREATMENT OF TUBERCULOUS ARTHRITIS

EUGENE KISCH[1]

We are tempted, when there is both a surgical and a conservative treatment available for a persistent disease, to use the former treatment, since an operation may possibly shorten considerably the time of treatment. This generally justified surgical point of view has to be subjected to a thorough critical review when we are dealing with the chronic disease of a joint, especially if the disease is tuberculous.

The general rule that any operation should be performed only when really indicated, applies in even greater measure to joint surgery. Any operation on a joint endangers, to a certain degree, the subsequent function of that joint. As a matter of fact, most surgical procedures in joint tuberculosis aim at completely eliminating the function of the joint. This results invariably in the crippling of the patient. On the other hand, we must realize that, no matter how efficient conservative treatment in joint and bone tuberculosis may be, it does not permit us to discard operations entirely. Rather, we have to supplement the conservative treatment with operations in many cases. Therefore the questions arise: Which operations are definitely necessary? What are the clinical indications for the necessary operations? Also, during what stage of the disease should these operations be performed? Which conservative treatment should we employ to avoid as far as possible a crippling operation?

First of all, we have to keep in mind that in a joint tuberculosis we are never dealing with a primary infection but always with a metastasis. Many tuberculous patients have acquired in their childhood a tuberculous infection in the lung with a secondary infection of the bronchopulmonary nodes. In most of these cases, the lesions of the primary complex do not produce clinical symptoms and become arrested. In contrast to the pulmonary focus, the infection in the lymph nodes may frequently reactivate and bacilli from such foci may enter the blood-stream and attack bones. Therefore, an operation can at best remove the metastatic focus but cannot completely cure the patient of his tuberculosis. To achieve this latter result it is necessary to cure the primary focus, the location of which often remains unknown, by treatment of the entire body over a prolonged period of time. The generally accepted fact that in bone tuberculosis we are always dealing with a secondary infection, has changed the type of operation employed. The previously held erroneous opinion that joint tuberculosis is a primary tuberculous infection resulted in the era of joint resections. Up to twenty-five years ago it was the accepted practice in all countries of Europe to remove the involved joints by resection. The justification for these far-reaching operations, which resulted in extensive crippling of the patient, was to cure the patient of his tuberculosis in a relatively short time. This erroneous assumption was bound to lead to bitter disappointment. A large percentage of

[1] Associate in Orthopedic Surgery at the Hospital for Joint Diseases, Far Rockaway, New York.

the patients suffered relapses or developed a new specific focus in another joint within a relatively short time after the operation.

As a consequence of the present-day acceptance of the idea of secondary infection in joint tuberculosis, resections are rarely performed and only on special indications, as will be noted later. Fusion operation has to-day taken the place of joint resections. In hip tuberculosis, extraärticular arthrodesis is recommended and a mixed type of arthrodesis is advised only when the X-ray evidence proves the presence of a sequestrum in the acetabulum or head or neck of the femur. Extraärticular arthrodesis is suggested in children only if they are more than 10 years old. In knee tuberculosis, intraärticular arthrodesis, in which sections of bone are removed from the tibia and femur, is recommended. To improve the effectiveness of the operation, Hibbs suggested the use of the patella as an extraärticular bone graft. As in hip tuberculosis, arthrodesis in tuberculosis of the knee should not be performed on children of less than 10 years of age.

A number of orthopedists recommend fusion operation, especially in hip and knee tuberculosis, as a matter of principle. They assume that immobilization of the afflicted joint is the only assurance against relapse and the only guarantee for painless functioning of the limb. This theory is accepted as so obvious that crippling of the patient is regarded as an unfortunate but an unavoidable fact. However, nobody would deny the tremendous advantage to the patient if the joint were to be healed with normal or practically normal mobility, even though the joint had formerly shown extensive destruction.

For this reason, we have investigated the following basic questions:

1: Is it possible to attain good active and passive mobility despite extensive destructio of the bone?
2: Will healing of a joint with good active and passive mobility guarantee a painless functioning of the limb?
3: Do more relapses occur in joints healed with mobility than in those healed with ankylosis?

The author studied these questions on 253 cases of knee tuberculosis at the University Institute for Joint and Bone Tuberculosis in Hohenlychen, Germany, from 1920 to 1929. Tuberculosis of the knee joint was selected for the test because it is more frequent and also because the functioning of the knee is of special importance in walking. The treatment of these cases consisted of a combination of conservative and surgical measures—as described below—which have to supplement each other in order to be effective.

When attempting to heal a tuberculous joint with mobility, we have to abandon first of all the traditional plaster cast. Our experience in a great number of cases has shown that, in order to be healed, the joint does not have to be immobilized, but only has to be relieved of its weight-supporting functions. Therefore, it is necessary that a patient suffering from tuberculosis of the hip, knee or ankle be confined to bed until he is healed. In tuberculosis of the hip and knee, traction has to be applied to prevent the development of muscular

cramps or deformities of the joints. Figure 1 shows traction in hip tuberculosis which is always applied on both sides. The pelvis rests on a cushion, four to five inches high, which is solidly stuffed with chopped straw. The involved hip joint is placed in abduction. A further important purpose of the traction is to correct pathological conditions as far as possible. If external rotation is present,

FIG. 1 Traction in external rotation

it is gradually corrected by the application of traction bandages. As will be seen in figure 1, the traction bandage is applied to the thigh and lower leg in such a way as to produce internal rotation; the weight suspended from the traction bandage should be between three to six pounds varying with the age of the patient. If we are dealing with an internal rotation, the traction bandages are applied in a contrariwise direction, producing external rotation.

Figure 2 demonstrates the traction bandages which we employ when a subluxation is present in knee tuberculosis. The calf is supported by means of a sling suspended from a wooden bar placed lengthwise over the bed. The sling must be placed just under the proximal end of the tibia. The knee itself is pulled downward by another sling from which are suspended two weights of two to five pounds each. The lower leg is pulled forward by a weight which is attached, via a pulley on the end of the bed, to a sleeve above the ankle.

After pain and muscular spasm have disappeared, we begin very cautiously with passive motion exercises, carefully avoiding any pain. In order to carry out successfully these motion exercises, the physician must have the necessary patience, and the patient, especially if a child, must have confidence in the steady and skilled hand of the doctor. These motion exercises not only maintain any existing mobility, but also restore lost mobility in a high percentage of cases.

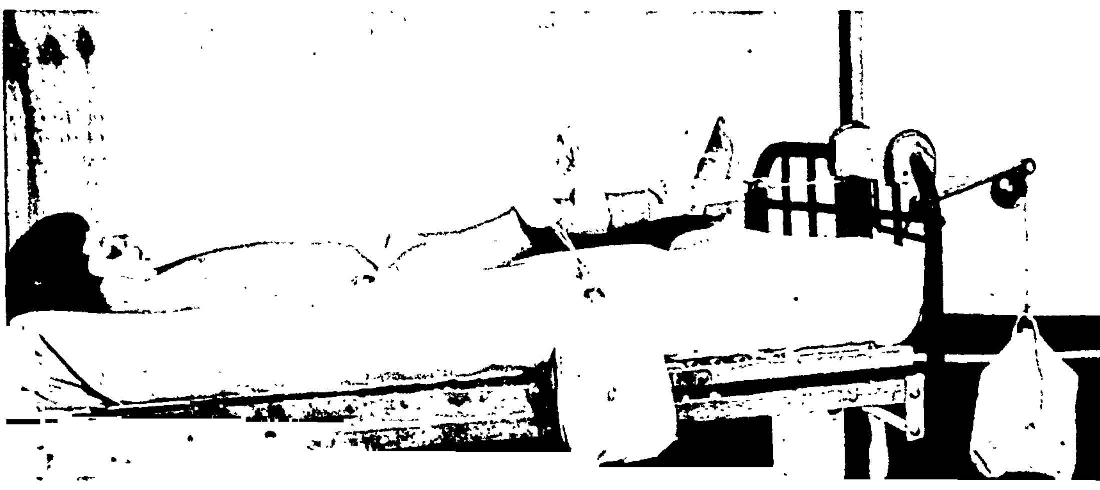


FIG. 2. Traction in subluxation

In the evaluation of the effectiveness of these measures, we have to keep in mind that the mobility of the limb has a practical value only after it has attained a certain degree. In the case of the knee joint, it is necessary that it can be actively stretched to normal extent and flexed to an angle of at least 130°. It is necessary, of course, that the patient be able to execute all movements without pain or muscle spasm. The latter, as a matter of fact, is in itself an important criterion of whether the joint has been healed or not. If the patient is unable to stretch the knee joint to normal extent, but is able to bend it to an angle of at least 130°, supracondylar osteotomy is indicated. However, this operation cannot bring about complete correction of the contracture if the angle of contraction is less than 120°, in which case an intraärticular arthrodesis should be performed. The latter operation is also recommended for patients in whom conservative treatment could not produce a flexion of less than approximately

140°, because such a limited mobility is more of a hinderance in walking than actual stiffness. Since all these corrective operations are to be performed after the involved joint is healed, it is necessary to remove only very thin sheets of bone from the condyles of the femur and tibia. As the removal of the latter is performed without touching the ephyseal line, it does not impede growth in children. In cases of subluxation which cannot be corrected by means of tractions, due to formation of osseous bridges the same type of intraärticular arthrodesis should be used. In cases of hip tuberculosis which have been healed with persistent contracture position in external or internal rotation, flexion or abduction, subtrochanteric osteotomy should be performed as a routine.

In tuberculous arthritis, operations are sometimes indicated in order to save the life of the patient; they will do this only if they are well timed. For example, we have to suspect a beginning amyloidosis if a patient with fistulous tuberculosis shows a gradually increasing albuminuria and if the general condition of the patient declines at the same time, and the skin becomes pallid and transparent. Even though all other tests may be negative, this suspicion must be entertained. Such a patient is condemned to die unless we free the organism of the focus of infection by extensive resection or by amputation of the entire limb. The same applies to patients with tuberculous arthritis with extensive destruction of the bone, further complicated by progressive pulmonary tuberculosis.

An old prejudiced view, which has been handed down, holds that in tuberculous arthritis the tendency of healing is considerably less in adults than in children and adolescents. For this reason, many orthopedists always recommend in adults intraärticular arthrodesis with simultaneous removal of the involved area of bone. The author, on the basis of the results he obtained with the therapy described in this article, cannot share this point of view. As will be seen in the statistics given later of the cases of knee tuberculosis treated in Hohenlychen, the tendency of healing is the same for adults, adolescents and children for hydrops and fungus, and is only insignificantly less in adults in osseous tuberculosis. The same holds true for the "lasting results" which are based on re-examinations over periods of as much as eleven years after the discharge of the patients from the hospital (6).

RELATION OF AGE TO HEALING

I. Hydrops

(a) At time of discharge: .. .. 12 cases

Age	*Number of Cases*	*Healed*
0–15	6	5
16–30	3	2
31–45	2	2
Over 45	1 (47 years)	0

(b) Lasting results (based on those healed or markedly improved)...... ...... 9 cases

Age	*Number of Cases*	*Healed*
0–15	5	5
16–30	2	2
31–45	2	2

II. Fungus

(a) At time of discharge: . . . . 79 cases

Age	Number of Cases	Healed
0-15	36	27
16-30	28	23
31-45	9	7
46-57	6	5

(b) Lasting results: . . . . 48 cases

Age	Number of Cases	Healed	Relapsed	Died
0-15	19	15	4	
16-30	21	18	2	1
31-45	5	4		1
46-57	3	3		

III. Osseous

(a) At time of discharge: . . . . 163 cases

Age	Number of Cases	Healed
0-15	61	41
16-30	69	48
31-45	25	10
46-60	8	4

(b) Lasting results: . . . . 92 cases

Age	Number of Cases	Healed	Improved	Relapsed	Died
0-15	38	29	2	7	
16-30	39	30	1	6	2
31-45	11	9		2	
46-60	4	3			1

Even though these statistics prove that the often held prejudice of a considerably smaller tendency of healing in adults is erroneous, there exists nevertheless a special indication for operation in adults. It is difficult, and often impossible, for men who are working and supporting their families to give up their jobs and spend a long time in a hospital in order to receive conservative treatment. In such cases, one is forced to perform extensive resections or amputations in order to shorten the length of time during which the patient is confined to bed. If these surgical procedures are not followed by conservative treatment of the entire body, we have to realize that relapse or the development of a new focus is well within the realm of possibility.

Extensive resections and amputations are further indicated in aged patients who have only a few years to live. It would be inadvisable to force the patient to spend a great part of his few remaining years in a hospital.

The presence of sequestra[2] plays a very important rôle in the indication for operation in tuberculous arthritis. In cases of tuberculous arthritis, the sequestrum is located in the region of, or even directly within, the epiphyseal line. Since this sequestrum formation usually occurs in children, the removal by operation would destroy the epiphyseal line partly or completely, and thereby disturb

[2] By a sequestrum is meant a piece of bone visible in an X-ray picture which has become completely separated during the process of necrosis from the surrounding osseous tissue.

the normal growth of bone. Our treatment results, in almost all cases, in the complete resorption of the sequestrum. The hyperemic effect produced by sunshine and passive congestion causes a speedy development of granulation tissue which attacks the sequestrum and results in its disintegration. This combination of active and passive hyperemia always produces, after the disintegration of the sequestrum, a rapid and complete filling-in of the cavity with new and normally structured bone tissue. Figure 3 shows a characteristic case of sequestrum resorption. We see here a destruction of the lateral condyle, epicondyle and the lateral half of the epiphyseal line of the femur. In the bone

FIG. 3. (Left) Destruction of lateral condyle, epicondyle and epiphyseal line. Three sequestra in condylar region, a fourth in the epiphyseal region. Guinea pig test positive. No sinus formation.

FIG. 4. (Right) Same case as figure 3, fourteen months later. Sequestra absorbed, cavity filled with new bone tissue. Epiphyseal line has reappeared.

cavity of the condylar region, there are three sequestra; a fourth one is located in the region of the epiphyseal line. Figure 4, taken fourteen months later, shows the stage of healing: all sequestra have been completely absorbed and the large bone cavity is filled with new, normally structured bone tissue. At the same time the destroyed part of the epiphyseal line has reappeared. The latter fact has enabled a normal bone growth, as proved by reëxamination over a long period of time.

A severe complication in tuberculous arthritis is the formation of abscesses. The abscess originates in the depth of the soft tissue and develops more and more towards the surface where it appears as a swelling. After disintegration of the subcutaneous tissue, the abscess breaks through the skin. In this way a sinus

is formed and greatly prolongs the time of treatment. A secondary infection, often caused by such sinus formation, has a devastating effect on the general condition of the patient. While a tuberculous abscess as such has no influence on the temperature of the patient, a secondary infection causes high fever. At the same time the patient loses appetite and weight and also suffers from insomnia. Mixed-infected tuberculous sinuses which exist over a long period of time cause amyloid formation in a number of cases. Since amyloidosis endangers the life of the patient, it is of prime importance to prevent the formation of sinuses. The formerly employed incision treatment of the abscesses is definitely to be avoided. We have observed the most severe secondary infections in cases where incisions of abscesses were performed prior to their admission to our hospital.

Fig. 5

Fig. 6

Figs. 5 and 6. Same case as figures 3 and 4. Active mobility after healing.

If we were able to prevent the formation of sinuses, we could not only considerably shorten the time of treatment, but also save a great number of lives. Sinus formation can be prevented only by puncture of the abscess, which should be performed as early as possible. Therefore daily examination of the involved part is necessary, especially during the phase of disintegration. One of the disadvantages of plaster casts is the prevention of such an examination. Consequently, we discover quite often a very advanced abscess, or even an abscess with sinus formation, after removal of plaster casts.

Tuberculous pus is usually thick, sometimes it is of the consistency of toothpaste and often contains flakes. Therefore, we need aspiration needles with diameters varying up to the size of a drinking straw. The opening in the bottom of the syringe has to be of the same diameter as the needle. During the phase of disintegration of the diseased area, two or three aspirations a week are the rule, and daily punctures are by no means rare. These continuous punctures have often resulted in sinus formation.

Twenty years ago, we developed a special technique for puncture of such abscesses which definitely prevents the formation of sinuses. The needle should be introduced into the skin about one inch above the upper border of the abscess. After the introduction, the needle is pushed forward into the subcutaneous tissue to a point above the centre of the abscess. Then, by raising the syringe, the needle is introduced into the abscess cavity. After removal of the needle, the point of skin puncture is so far from the point of entry into the abscess that after-flow of pus cannot occur. The after-flow of pus is further prevented by the two sharp bends at either end of the passage (6).

Employing this technique, we have punctured many hundreds of abscesses, most of them twenty or forty times, and many of them over ninety times. These punctures were always performed without causing sinus formation, except for very rare cases. In these cases we were unable to prevent the formation of sinuses because at the time of admission of the patient to our hospital the skin covering the abscess was already too thin.

We must now consider the conservative treatment that most strengthens the whole body for the victorious fight against the tuberculous infection. This treatment should cover not only the involved joint, but also the entire body, including the primary focus, the location of which often remains unknown. Another prerequisite of the treatment is that it should limit the operations required to the above-mentioned strict indications. Only the action of a great stimulant enables the weakened body to overcome the tuberculous infection. One such stimulant, the sun-rays, was already known to the ancient Romans and Greeks, who considered the influence of sunshine and fresh air to be the fundamental basis of all physical and mental well-being. The Romans built gardens on the roofs of their homes where they took sunbaths in complete nudity. In modern times Bernhard (1) and later on Rollier (11), in the Swiss mountains, were the first to prove that the sun-rays have a therapeutic influence on joint and bone tuberculosis. This method of treatment, with its excellent results, was not to be limited to those who could afford the extended stay in the Swiss mountains. Therefore, the author studied for a longer period of time in Rollier's hospital in Leysin, Switzerland, the following questions: (*1*) Can heliotherapy be transferred from the high mountains to the flatlands? (*2*) Can the very extended time of treatment be considerably shortened by a combination of heliotherapy with other forms of treatment?

Solar radiation, as we have proved by clinical observation and by experimental measurements, causes a marked hyperemia in the high mountains as well as in the flatlands. The effect of the hyperemia is by no means limited to the skin but, on extended therapy, penetrates into deeper tissues, namely the muscles and bones.

The first effect of hyperemia, which can be clinically observed, is the gradual disappearance of pain in the involved joint. Tuberculous joints are often quite painful and their characteristic contracture position is largely caused by pain. Simultaneously with the disappearance of pain, the flexed position of the diseased joint gradually decreases, especially if traction is applied at the same time.

A further proof of the hyperemic effect of solar radiation is its influence on the tuberculous focus itself. As can be seen in series of X-ray films taken two months apart (6), this hyperemia causes a gradual disintegration of the bone focus. This stage is often characterized by the formation of abscesses in the area of the involved joint or by increased discharge of pus from already present sinuses. The second stage of the hyperemic effect of solar radiation sets in only after disintegration of the whole diseased bone tissue, which is often more extensive than revealed by X-ray appearance. This phase is marked by regeneration of bone.

In order to shorten the time required by heliotherapy, we have augmented the hyperemic effect of solar radiation by inducing passive congestion with Bier's rubber-bandage method. In cases of tuberculosis of the extremities we apply the rubber bandage for two four-hour periods daily.

It is important that the patient be gradually acclimatized to heliotherapy. Therefore, we do not expose the diseased part to the sunshine until after all other parts of the body have been exposed. To achieve this, we start with exposing the feet and gradually advance until we include the whole body (5).

Up to a short time ago, the presence of active pulmonary tuberculosis was thought to be a contraindication against heliotherapy. Because we cannot predict the possibility of a pulmonary hemorrhage through clinical or X-ray examination, it was thought inadvisable to expose a patient with active pulmonary tuberculosis to the hyperemic effect of solar radiation. This danger of hemorrhage can be eliminated by employing an especially cautious schedule of acclimatization of the patient to heliotherapy (8). Heliotherapy should be employed only under constant medical supervision and should not be used if the patient is in the febrile state. A great number of patients on whom we have performed phrenic exeresis or thoracoplasty were treated prior to the operation with heliotherapy. The time required for convalescence after the operation was considerably shortened by continuing heliotherapy.

Heliotherapy should be combined with open-air treatment because open-air has the same stimulating effect on the organism as the sun-rays. Both should be used complementing each other, whether it be in the high mountains or in the flatlands. Therefore, it is very advisable that the patients spend sunless days on a half-covered porch and also sleep there on summer nights. The interruption of either the sunshine or open-air treatment not only extends considerably the time of treatment but also endangers results already achieved. Halsted of the Johns Hopkins Hospital was the first to use exclusively open-air treatment for tuberculous arthritis (4); Halsted carried out the open-air treatment throughout the whole year, day and night, and therfore was able to call his treatment a true "twenty-four-hours-a-day-out-of-doors" treatment. He reported remarkable results, especially as far as the mobility and functional use of the afflicted limb are concerned.

Next to the lung, the skin is the most important respiratory organ. Thus, the effect of the open-air treatment is considerably decreased if on cold days the patient is completely covered by blankets. The author has developed an irradiation lamp system by which we can expose the patient in complete nudity on a

half-open porch even in the coldest weather, and enable the patient to obtain the fullest benefit from the open-air treatment (6). This system has a carbon arc lamp producing a spectral emission which is very similar, both quantitatively and qualitatively, to the sun-spectrum. Eight beds are arranged in star-like position around this arc lamp. Above each bed there are two heating units, one above the chest and the other above the inguinal region of the patient. The heat produced by these heating units enables the completely nude patient to lie on the porch in full comfort, even on the coldest days. In order to compensate for outside temperature variations, these lamps are adjustable, that is, they can be lowered or raised according to these variations.

In order to prevent relapses it is of great importance to harden the patient against the rigors of his native climate. For this reason, we attempt gradually to acclimatize the patient to raw climatic conditions by adding an electric fan to each side of the system. Each fan has four different speeds and as the local and general conditions improve we gradually increase the fans' speed.

Another form of radiation which we frequently employ is X-ray. We use it as a valuable addition to our other therapeutic measures. We administer X-rays in small dosages; the patient is given $\frac{1}{10}$ of the skin-erythema-dosage twice a week until the whole skin-erythema-dosage has been administered. As a rule, a second course is given after a period of six weeks. This form of X-ray therapy gives especially favorable results in (*1*) tuberculous lymph nodes, (*2*) the synovial form of tuberculous arthritis, (*3*) cases of sinuses existing for a long time.

Employing the operative and conservative measures described above, we have treated 253 cases of knee tuberculosis from 1920 to 1929. They were made up of 11 cases of hydrops, 79 fungous cases and 163 cases of osseous tuberculosis. These patients were of all ages (102 cases of 1 to 15 years, 100 cases of 16 to 30 years, 15 cases above 45 years of age). The clinical and roentgenological diagnoses were confirmed by tuberculin tests and by microscopic examination and guinea pig tests of all fluids and abscess contents. Only cases in which the diagnosis was definitely established were included in these statistics.

As stated at the beginning of this article, we shall try to answer on the basis of the statistical results of these 253 cases of knee tuberculosis the following important questions: Is it possible to attain good active and passive mobility despite extensive destruction of the bone? Will healing of a joint with good active and passive mobility guarantee a painless functioning of the limb? Do more relapses occur in joints healed with mobility than in those healed with ankylosis? We have compiled the results of these cases, successful and unsuccessful, into detailed statistics. These data are divided into the three different types of knee tuberculosis mentioned above and show the percentage of "healed,"[3] "markedly improved," "unchanged" and "died" cases in each group. In the latter cases we report the cause of death.

[3] The term "healed" in our statistics signifies disappearance of all clinical symptoms (pain, muscle tenderness, sinus, temperature etc.). Furthermore, there must be roentgenological proof of the healing of the lesion (sharply defined borders of the area, filling up of the original focus with new bone tissue of normal structure, disappearance of the bone atrophy, complete disappearance of any abscess or calcification of the remnants).

Due to the lack of space, it is impossible to reproduce here in totality these detailed statistics. It is inadvisable, as a matter of principle, to reproduce any given statistics in part because that often leads to an erroneous interpretation of the results. For this reason, I have to refer the reader to the complete statistics (6). The three questions asked above are answered in the section of the statistics dealing with reëxamination of all patients released as "healed" or "markedly improved." These reëxaminations were carried out over a period of many years, in some cases up to eleven years after the release of the patient from the hospital.

These data prove that normal or functionally adequate[4] mobility was attained in 100 per cent of the hydrops cases, in 60 per cent of the fungous cases and in 28.4 per cent of the osseous cases. A relatively high percentage of osseous cases were healed with ankylosis. This was caused by the fact that most of the cases were unusually severe at the time of admission, with 30 per cent of them already showing bony ankylosis at that time. The statistics of "lasting results" demonstrate further that, of the 6 fungous and 15 osseous cases which relapsed, 14 had been healed with ankylosis, 7 with adequate function and that not a single case with completely restored mobility had relapsed.

The reëxaminations proved also that a joint healed with mobility does not fatigue more easily than an ankylosed joint and that it does not become painful on use. As a matter of fact, the cured patients were able to resume their former occupations, as farmers or factory workers, and were also able to go on extensive hikes, climb mountains and ride bicycles.

It should be pointed out that children, as well as adults, who suffer from shoulder, elbow, wrist, finger, rib or lymph node tuberculosis do not have to be hospitalized. For the treatment of these patients, the author founded in Europe the Ambulatory Institute (7). The latter was located in the heart of the workers' district of Berlin and was surrounded on all sides by playgrounds. In this Institute the patients received identically the same treatment as described above, the only difference being that the patients arrived in the institute daily (except Sundays) at 8:00 a.m. and left there at 5:00 p.m. At the Institute, the children received five hours of open-air class-room instruction everyday, so that their intellectual development would not be retarded. The results obtained were so satisfactory that two branches were opened in other worker districts of Berlin and Ambulatory Institutes were built in Rome and Moscow. During a lecture trip in 1944, the author introduced the idea of the Ambulatory Institute into Brazil, where the health authorities are now planning to construct similar institutes (9).

Bernhard and Rollier reported at the beginning of this century the excellent results they obtained in joint and bone tuberculosis with heliotherapy in the Swiss high mountains. Both Bernhard and Rollier drew the erroneous conclusion that these results were caused only by the action of the sun-rays and that the latter are of sufficient therapeutic effect only in the high mountains. The author

[4] "Functionally adequate" signifies full normal extension and flexion of at least 90°.

was able to prove that solar radiation in the flatlands has the same therapeutic effect as in the high mountains and that, in addition, open-air treatment during the winter has the same stimulating effect as heliotherapy during the summer. The validity of our conclusion is proved by the above-mentioned results which Halsted obtained through his exclusive use of open-air treatment in the flatlands.

Our experience has further shown that patients who cured in the high mountains have a greater tendency to relapse than those who cured in the flatlands. For this reason it is advisable that bone and joint tuberculosis should be treated in the same climate in which the disease was contracted (5, 6). The same applies to pulmonary tuberculosis and Pinner (10) concludes that "the patient with pulmonary tuberculosis is as a rule best treated in the climate in which he has to live after his cure." Optimum results can only be achieved through sunshine and open-air treatment if all necessary facilities are available, and, even more important, if the treatment is carried out faithfully day by day in summer as well as in winter.

Heliotherapy and open-air treatment should not extend beyond the point where surgical measures are indicated. On the other hand, operations should not be performed which could be avoided by use of this conservative treatment. A "matter of principle" treatment, either conservative or surgical, is harmful to the patient and should be rejected.

SUMMARY

1. The treatment of tuberculous arthritis, in children and adults, is discussed.
2. A review and evaluation of reported conservative and surgical measures are presented.
3. A treatment, consisting of heliotherapy, open-air treatment, traction and surgical measures, is described.
4. In a high percentage of cases, the proposed treatment results in restoration of mobility in the afflicted joints.
5. It is shown, on the basis of 253 cases of knee tuberculosis, that good active and passive mobility can be attained despite extensive destruction of the bone.
6. The conclusion is reached that, in the treatment of tuberculous arthritis, conservative and surgical measures have to supplement each other. A "matter of principle" treatment, either conservative or surgical, is harmful to the patient and should be rejected.

SUMARIO

1. En esta reseña del tratamiento de la artritis tuberculosa en los niños y adultos preséntanse un repaso y una justipreciación de las medidas conservadoras y quirúrgicas comunicadas hasta ahora.
2. Descríbese un tratamiento que consiste en la helioterapia, el empleo del aire libre, la tracción y ciertos procedimientos quirúrgicos.
3. En un porcentaje elevado de los casos, el tratamiento propuesto restablece la movilidad de las articulaciones afectadas.

4. Tomando por base 253 casos de tuberculosis de la rodilla, demuéstrase que puede alcanzarse buena movilidad activa y pasiva, a pesar de extensa destrucción del hueso.

5. Sácase la conclusión de que en el tratamiento de la artritis tuberculosa las medidas conservadoras y quirúrgicas tienen que complementarse. Todo tratamiento a base absoluta, ya sea de conservadurismo o cirugía, resulta nocivo para el enfermo y debe ser rechazado.

REFERENCES

(1) Bernhard, O.: Sonnenlichtbehandlung in der Chirurgie, Ferdinand Enke, Stuttgart, 1917.

(2) Gaugele, K.: (a) Zur Behandlung der Gelenktuberkulose, insbesondere der Coxitis, Chirurgie, 1930, *2*, 163. (b) Frühzeitige Mobilisierung bei Knochen- und Gelenktuberkulose, Verhandl. d. deutsch. orthopaedischen Gesellsch., 1929, *23*, 314.

(3) Girdlestone, G. R.: Tuberculosis of Bone and Joint, Oxford University Press, London, 1940.

(4) Halsted, W. S.: Results of the Open-air Treatment of Surgical Tuberculosis, The National Association for the Prevention of Tuberculosis, Tavistock House, London, 1905.

(5) Kisch, E.: Diagnostik und Therapie der Knochen- und Gelenktuberkulose, F. C. W. Vogel, Leipzig, 1925 (2nd ed.).

(6) Kisch, E.: Contributor of chapter 26, Radiation and Climatic Therapy of Chronic Pulmonary Disease, William & Wilkins Co., Baltimore, 1944.

(7) Kisch, E.: Medizin, Gymnastik und Paedagogik im Kampfe gegen die Tuberkulose, Georg Thieme, Leipzig, 1930.

(8) Kisch, E.: Die Strahlenbehandlung der chirurgischen Tuberkulose, Strahlentherapie, 1928, *28*, 227.

(9) Kisch, E.: Prevenção da tuberculose, Rev. brasil. de med., 1945, *2*, 74.

(10) Pinner, M.: Pulmonary Tuberculosis in the Adult, Charles C. Thomas, Springfield, 1945.

(11) Rollier, A.: Die Heliotherapie der Tuberkulose, Julius Springer, Berlin, 1913.

CLOSED INTRAPLEURAL PNEUMONOLYSIS AND THORACOSCOPY[1]

G. H. C. JOYNT

Since the introduction of closed intrapleural pneumonolysis by Jacobaeus in 1913, this procedure has become a highly valuable operation in the surgical therapy of pulmonary tuberculosis. The production and maintenance of a satisfactory pneumothorax is accepted as one of the most adequate forms of collapse therapy. Hence the use of thoracoscopy and pneumonolysis is frequently indicated in the initial stages of artificial pneumothorax treatment of pulmonary tuberculosis. In 1934, Moore published a report on a collected series of 2,043 cases of intrapleural pneumonolysis and, in the following ten years, Goorwitch compiled a further series of 5,114 cases from the English and American literature.

Although intrapleural pneumonolysis may frequently produce an efficient selective collapse, the complications attributable to the operation must be thoroughly considered. Many reports of postoperative development of fluid, either serous or purulent, have been published. Dickey, however, has pointed out that the incidence of tuberculous empyema following intrapleural pneumonolysis may be less than the incidence in some series following pneumothorax without section of adhesions. Complications frequently occur in the maintenance of an ineffective pneumothorax which may produce clinical improvement for a time. In these cases the early use of thoracoscopy and pneumonolysis is necessary. It is the opinion of the staff of the Queen Alexandra Sanatorium that the early abandonment of an ineffective pneumothorax is essential in the treatment of pulmonary tuberculosis.

Thompson and Greenburg have pointed out that, following initial pneumothorax, the pleura is pale and shiny and at this time adhesions are easily divided along the line of cleavage in the endothoracic fascia. If an effusion forms in the pneumothorax cavity, the pleura becomes dull and thickened and the adhesions firm, fibrous and thickened. As a result, the operation is made more difficult and hazardous. It is important, according to Thompson and Greenburg, that pneumonolysis be carried out within six weeks following the initiation of pneumothorax. Formerly, it was the custom to push a pneumothorax to stretch and thin out the adhesions. This treatment has also been recommended following pneumonolysis but has proved to be a dangerous procedure. Further stages are indicated within a few weeks if a satisfactory pneumothorax is not obtained following an initial pneumonolysis. In our experience, early operation has decreased the complications and lessened the technical difficulties of operation, as well as promoted an early effective collapse.

PNEUMONOLYSIS

This review includes 277 consecutive cases of closed intrapleural pneumonolysis and 44 cases of thoracoscopy. The operations were performed at the Queen Alexandra Sanatorium over a period of six years extending from 1938 to April, 1944.

[1] From the Queen Alexandra Sanatorium, London, Ontario, Canada.

In all cases in which adhesions were cauterized (277 cases) the galvanocautery was used with the two cannulae technique. As shown in table 1, there was a total of 348 stages of which 92 had complete operation with freeing of all adhesions to the involved lobe. The remainder, according to the classification as outlined by Goorwitch, included 136 incomplete and 114 partial pneumonolyses. In most cases the surgical procedure was limited to one hour or less, since it was found that the patient was less disturbed and the operative technique was better and more accurate when the operation was not prolonged. The more difficult and complicated cases were done in two or three stages unless dangerous tension was present on a portion of lung. Carp has pointed out that the division of adhesions requires patience and meticulous care and any attempt to hurry may produce disastrous complications or incomplete therapy.

In the cases with a low respiratory reserve and in some cases of bilateral pneumothorax, it has been noted that following pneumonolysis the patient complained of considerable discomfort in the chest and of moderate dyspnea. This has been lessened in many cases by the withdrawal of the open trochar at the height of expiration following the operation. It is well known that the intrapleural pressures are lower after an open pneumothorax is closed at the height of expiration than after closure during inspiration. In order to insure negative pressures in the pneumothorax cavity, after pneumonolysis and thoracoscopy, aspiration of air has been carried out on the last 192 consecutive cases at the end of operation. This was done on the operating table and air was aspirated until the intrapleural pressures were definitely negative. In this group of cases no pneumothorax has been lost and the patients have been much more comfortable postoperatively. In only 3 cases has a refill been required on the first postoperative day and the average time for a refill following operation in this group has been three and one-half days. Surgical emphysema also has been reduced although 3 cases of severe emphysema occurred in patients with thin chest walls and severe cough.

TABLE 1

Closed intrapleural pneumonolysis

Total number of cases		277
Total number of stages		348
Type of operation	Complete	92 (26%)
	Incomplete	135 (39%)
	Partial	113 (33%)
	Unknown	8

POSTOPERATIVE COMPLICATIONS AND RESULTS OF PNEUMONOLYSIS

As frequently pointed out, the most important complication which occurs following closed intrapleural pneumonolysis is the development of pleural fluid. In this report all clear and slightly cloudy fluid is classified as serous, except cloudy effusion with tubercle bacilli on direct smear which is considered purulent. In

table 2, it is shown that the incidence of empyema is 5.8 per cent. Two of these cases occurred in patients with silicosis and pulmonary tuberculosis. It has been estimated by D. W. Crombie that the incidence of empyema in the pneumothorax treatment of silico-tuberculosis is approximately 90 per cent and as a result pneumothorax therapy in silicosis complicated by pulmonary tuberculosis has been abandoned at the Queen Alexandra Sanatorium. If these 2 cases of silico-tuberculosis are excluded the incidence of empyema is reduced to 5.1 per cent.

There were 77 cases of postoperative serous effusion (table 2). These are classified into three groups—slight, moderate and gross. Only 31 of this group were aspirated and in 9 patients the fluid was negative on culture for tubercle bacilli. One of these cases developed an obliterative pleuritis and required oleothorax, but the remainder obtained a satisfactory collapse although one pneumothorax was purposely reëxpanded three years following operation for tuberculous bronchitis. The group of 22 cases with tubercle bacilli on concentration or culture in the pleural fluid, obtained a satisfactory pneumothorax in 12

TABLE 2

Postoperative complications of pneumonolysis

*Purulent effusion—16 cases	Pure tuberculosis	15	(5.8%)	
	Mixed	1		
Serous effusion—77 cases	Slight	42	(15.1%)	27.8%
	Moderate	25	(9.0%)	
	Gross	10	(3 6%)	
Spontaneous pneumothorax		2	(0.7%)	
Hemothorax		1	(0.36%)	

* Two cases occurred in silico-tuberculosis (14 cases — 5.1%)

cases (one case was also reëxpanded following operation, on the diagnosis of tuberculous bronchitis). Two cases developed obliterative pleuritis and the remaining 8 cases had an unsatisfactory pneumothorax (6 of these required thoracoplasty).

According to Goorwitch, the great majority of complications attributable to pneumonolysis occurred within the first four postoperative weeks. In the complications listed in table 2, 11 of the 16 empyema cases developed a pleural effusion within one month and the remainder ranged from three months to two years. Approximately 80 per cent of the serous effusions occurred one month postoperatively, although it is interesting to note that only 12 of the 22 positive effusion cases developed fluid within the four-week period. The remaining complications included 2 cases of spontaneous pneumothorax and one case of hemothorax.

Although the great majority of complications occurred in the partial or incomplete operations, it will be noted from table 1 that only 26 per cent of the total

stages were complete and in a few cases it was necessary to do two or three stages to free the adhesions. Frequently a satisfactory and efficient pneumothorax is obtained with partial and incomplete operations. Many of the complications and poor results following pneumonolysis are due to prolonged pneumothorax therapy in the presence of an inefficient pneumothorax.

In evaluating the results it is of interest to point out the preoperative diagnosis in this group of 277 cases. According to the National Tuberculosis Association classification there were 13 minimal, 60 moderately advanced and 204 far advanced cases. Over 50 per cent of the patients had cavitation 2.5 cm. or over in diameter and 32 cases (11.6 per cent) showed cavities over 5 cm. in diameter. As expected, the complications were greater in the cases with large cavities, but an efficient pneumothorax was obtained in 19 of the 32 cases with large cavities.

In the entire series, there was conversion of sputum to negative cultures in 165 cases as well as 28 cases with negative cultures previous to pneumonolysis in which adhesions were divided to insure adequate collapse. Thus, a total of 70 per cent of this series obtained negative sputum cultures and a further 5 per cent were discharged as quiescent with positive cultures. Tuberculous bronchitis

TABLE 3

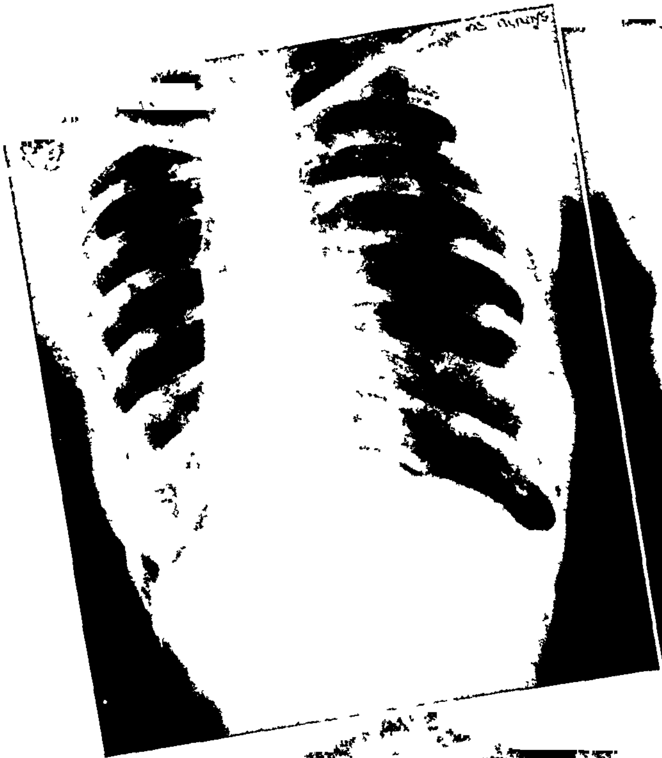
Sputum results following pneumonolysis

Converted to negative cultures	165 cases (60%)	70%
Negative cultures previous to operation	28 cases (10%)	
Positive cultures—patients discharged as quiescent	20 cases (7%)	

was diagnosed following pneumonolysis by bronchoscopic examination in 8 cases.

THORACOSCOPY

Thoracoscopy has been carried out in 44 patients. Not infrequently the adhesions were viewed from both a posterior and anterior cannula to determine the possibility of cauterization. In this group there were no postoperative complications in 36 cases, mild fever in 4 cases for two or three days and slight increase in a previous effusion in 2 cases which gradually subsided. A gross effusion developed in one patient nine months after thoracoscopy which revealed inoperable adhesions in the apex. One other patient, following a partial pneumonolysis in an attempt to close a large cavity, developed a small effusion with low grade fever which persisted. Two months following pneumonolysis, a thoracoscopy was performed and, one month later, the patient developed a slight increase in the pleural effusion. In a few months the fluid became positive for tubercle bacilli and thoracoplasty was performed. In view of these circumstances, it was felt that the empyema was not directly attributable to thoracosopy.



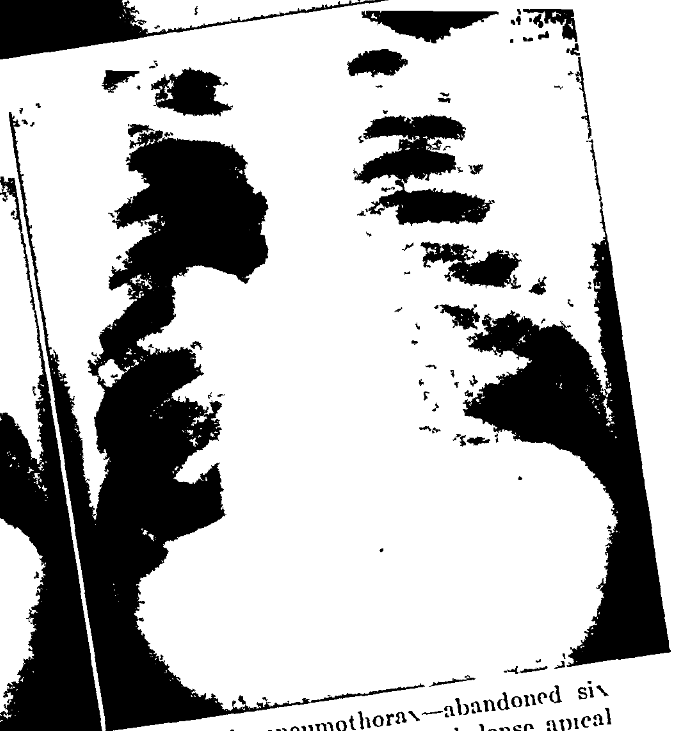


Fig 1a. (Upper left) G. M. Age 26. Previous left pneumothorax—abandoned six years Inefficient right pneumothorax with patent upper lobe cavity and dense apical adhesions

Fig 1b (Upper right) G M Following two-stage right pneumonolysis, satisfactory pneumothorax with cavity closure.

Fig 2a. (Lower left) A M. Age 18 Extensive dense upper lobe adhesions with large patent cavity

Fig 2b (Lower right) A M After two-stage left pneumonolysis, selective upper lobe collapse with cavity closure.

As repeatedly pointed out by many authors, the number and types of adhesions cannot be reliably determined from radiographic and fluoroscopic examination. The only satisfactory way to determine whether pneumonolysis is feasible is to perform a thoracoscopic examination. (See figures 1 and 2.) In this way an efficient pneumothorax may be quickly attained or an unsatisfactory pneumothorax abandoned early. The use of thoracoscopy appears to be a safe and conservative measure in collapse therapy.

SUMMARY AND CONCLUSIONS

A series of 277 cases of closed intrapleural pneumonolysis (348 stages) and 44 thoracoscopies is presented.

Early cauterization of adhesions is indicated and early abandonment of an inefficient pneumothorax is recommended.

Aspiration of air following operation increases the comfort of the patient and reduces surgical emphysema.

The most frequent complication is the development of pleural fluid, usually occurring in the first month. The incidence of empyema was 5.8 per cent in this series.

A satisfactory and efficient pneumothorax was obtained in 77 per cent of cases (70 per cent obtained negative sputum on culture).

Thoracoscopy is a safe and efficient procedure and its early use in pneumothorax therapy is advocated.

SUMARIO Y CONCLUSIONES

Preséntase una serie de 277 casos de neumonolisis intrapleural cerrada (348 etapas) y 44 toracoscopias.

La cauterización temprana de las adherencias está indicada y se recomienda el abandono temprano de todo neumotórax ineficaz.

La aspiración de aire después de la operación aumenta la comodidad del enfermo y reduce el enfisema quirúrgico.

La complicación más frecuente consiste en la aparición del líquido pleural, por lo general en el primer mes. En esta serie la incidencia del empiema llegó a 5.8%.

En 77% de los casos obtúvose un neumotórax satisfactorio y eficaz (70% mostraron esputos negativos en los cultivos).

La toracoscopia constituye un procedimiento inocuo y eficaz y se aconseja su empleo temprano en la colapso-terapia.

BIBLIOGRAPHY

(1) Alexander, John: The Collapse Therapy of Pulmonary Tuberculosis, Charles C. Thomas, Springfield, Illinois, 1937, p. 290.

(2) Anderson, R. C., and Alexander, John: Closed and open intrapleural pneumonolysis, J. Thoracic Surg., 1937, *6*, 502.

(3) Brock, R. S.: Thoracoscopy and cauterization of adhesions, Brompton Hospital Reports, Vol. VII, 1938.

(4) Brunn, H., Bull, S., and Prinzmetal, M.: Factors altering intrapleural pressure and their clinical significance, J. Thoracic Surg., 1932, *1*, 243.

(5) Carp, L., and Kornblith, B. A.: Thoracoscopy and pneumonolysis, Surg., Gynec. & Obst., 1942, *74*, 939.
(6) Crombie, D. W.: Personal communication.
(7) Custer, E. W., and Cohen, A. C.: The incidence of empyema following intrapleural pneumonolysis, J. Thoracic Surg., 1941, *10*, 625.
(8) Cutler, J. W.. Principles of pneumonolysis, Surg., Gynec. & Obst., 1937, *64*, 820.
(9) Dailey, J. E.: Intrapleural pneumonolysis, Dis. of Chest. 1943, *9*, 482.
(10) Dickey, A. B.: Empyema, Am. Rev. Tuberc., 1943, *48*, 222.
(11) Drash, E. C.: An appraisal of closed internal pneumonolysis in pulmonary tuberculosis, J. Thoracic Surg., 1938, *7*, 411.
(12) Goldman, A.: A method of preventing and controlling subcutaneous emphysema following closed intrapleural pneumonolysis, J. Thoracic Surg., 1939, *8*, 226.
(13) Goorwitch, J.: Complications of closed intrapleural pneumonolysis, Am. Rev. Tuberc., 1943, *48*, 205.
(14) Goorwitch, J.: Thoracoscopy in pulmonary tuberculosis, J. Thoracic Surg., 1943, *12*, 361.
(15) Goorwitch, J.: Closed intrapleural pneumonolysis, J. Thoracic Surg., 1944, *13*, 223.
(16) Matson, R. C.: Intrapleural pneumonolysis by the closed method, Am. Rev. Tuberc., 1939, *39*, 126.
(17) Moore, J. A.: Intrapleural pneumonolysis, J. Thoracic Surg , 1934, *3*, 276.
(18) Newton, H. F.: Intrapleural pneumonolysis, Am. Rev. Tuberc., 1940, *41*, 22.
(19) Scarborough, C. G.: Thoracoscopy, Am. Rev. Tuberc., 1939, *40*, 389.
(20) Stemmermann, M., and Tchertkoff, L.: Complications of closed pneumonolysis, Quart. Bull. Sea View Hosp., 1940, *5*, 421.
(21) Thompson, S. A., and Greenburg, M.: Jacobaeus operation, Am. Rev. Tuberc., 1941, *44*, 183.

LATENT SILICOSIS AND TUBERCULOSIS[1]

HOWARD DAYMAN

Clinical and experimental studies have shown that silicosis renders the patient more susceptible to tuberculosis. The degree of silicosis required to bring about this alteration in resistance is not clearly defined, yet the problem is important both from a clinical and from a medico-legal standpoint. The following 4 case reports bear evidence that silicosis can exert a harmful effect on resistance to tuberculosis even when generalized pulmonary fibrosis due to free silica is so slight that evidence of it is meagre or entirely lacking on technically satisfactory roentgenograms. For the purpose of this report, the condition has been designated latent silicosis.

CASE HISTORIES

Case 1: In 1930, G. D., age 34, engaged for a few months in the milling of tremolite, a chemical allied to asbestos, and later was a mucker in an anthracite mine for a similar period. In April, 1935 the patient became a pneumatic driller at a zinc mine where there is known to be a silicosis hazard. A chest roentgenogram made at the inception of this last employment gave evidence of a few small calcified lesions in both lungs and in the hilar lymph nodes, presumably the result of childhood tuberculosis. The patient developed a pleural effusion on the right side in 1939 but after a brief period resumed work as a driller. In May, 1941 he stopped work because of illness and was admitted to Ray Brook in July, 1941. Examination showed the presence of disease limited to the right lung and complicated by pleurisy. Tubercle bacilli were later found in the sputum. The roentgenograms (figure 1a) made at the time of entrance were submitted to three consultants, experienced in pneumonoconiosis, who concurred that there was no evidence of silicosis, an opinion with which we at that time agreed. The left lung field in particular presented neither the small, widely distributed shadows indicative of silicotic nodulation nor exaggeration of the linear markings. In view of the short exposure to dust, it was reasonable to conclude that the dosage of silica had been insufficient to produce either generalized nodulation or demonstrable linear fibrosis.

Approximately one year later minute shadows gradually appeared in the left lung field (figures 1b and 1c[2]) and were erroneously attributed to miliary tubercles. The patient developed pulmonary heart disease with decompensation and died in January, 1943, one and a yalf years after entering the hospital and four years after the original attack of pleurisy.

Autopsy disclosed conglomerate silico-tuberculous lesions in the apex and base of the right lung. A multilocular antrum was present in the right apex, communicating with the right pleural space which was the site of a mixed infection empyema. Scattered throughout the left lung were numerous silicotic nodules many of which showed evidence of tuberculosis as well. Tuberculous disease was predominantly situated within or adjacent to the silicotic lesions. Numerous asbestos bodies, in this case due to tremolite, were present in the tissues. The loose cellular connective tissue about bronchioles and blood vessels and in pulmonary septa was likewise probably due to the action of tremolite.

[1] From New York State Hospital for Incipient Pulmonary Tuberculosis, Ray Brook, New York.

[2] Figure 1c shows midportion of left lung field, enlarged.

Case 2: E. J., age 36, had been a mucker in a tremolite mine for one year and a driller in a zinc mine for approximately thirteen years, discontinuing the last mentioned employment in June, 1939 because of outspoken local and constitutional symptoms attributable to pulmonary tuberculosis. There were mott'ed shadows at the summit of

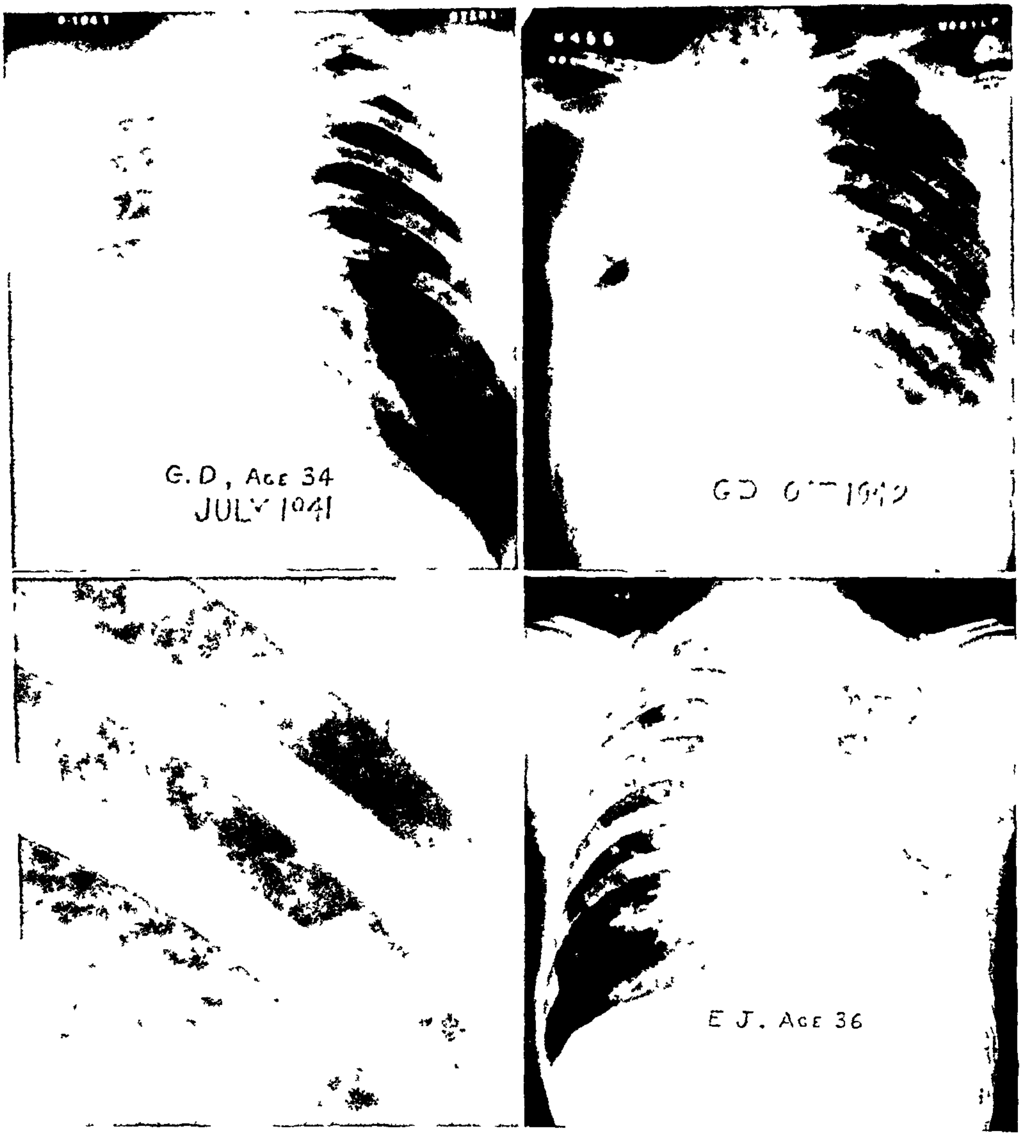


Fig. 1a (upper left), Fig. 1b (upper right), Fig. 1c (lower left) and Fig 2 (lower right)

both lung fields and tubercle bacilli were present in the sputum. Linear markings were prominent throughout the lung fields but there were no shadows compatible with generalized silicotic nodulation Therefore a claim for compensation was disallowed, and the *case closed, on the grounds that there* was no medical evidence to indicate that the claimant's disability was in any way related to his employment. This decision was based on authoritative medical opinion.

The disease rapidly progressed. Numerous minute shadows appeared on the roentgenogram in all areas not occupied by larger mottled shadows (figure 2). A diagnosis of silicotuberculosis was made. Pulmonary heart disease with decompensation developed and the patient died in April, 1943, approximately four years after the onset of symptoms.

Autopsy disclosed nodular and conglomerate silicosis together with tuberculosis.

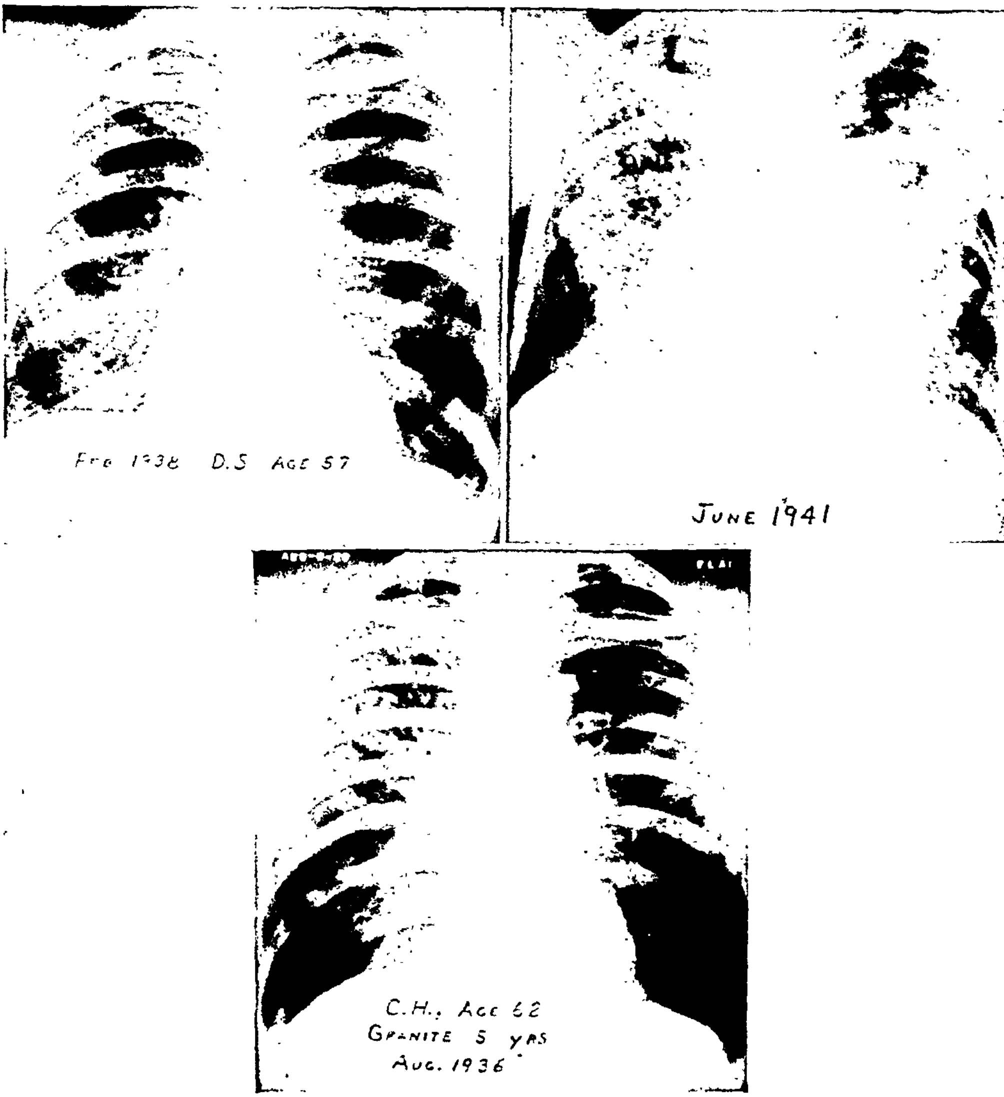


FIG. 3a (upper left), FIG. 3b (upper right), and FIG. 4 (bottom)

The reaction to tremolite was similar to that observed in the first case. The tuberculous disease was "largely localized in and about the silicotic lesions." "In this case the causal relationship between the occupational dust reaction and the superimposed infection is unusually well defined."[3]

[3] Quoted from the autopsy report of Doctor Gardner who made the pathological examinations in each of the 4 cases.

Case 3: D. S., age 57, had been a mucker in a magnetite mine for twenty-seven years. Though feeling perfectly well in February, 1938, a routine chest roentgenogram presented a few abnormal shadows at the right apex and in the left first interspace indicative of tuberculosis (figure 3a). There was generalized exaggeration of the linear markings but no distinct evidence of silicotic nodulation. Pulmonary fibrosis due to silica was thought to be so slight as to have no bearing on the tuberculous condition.

In December, 1939 the patient entered Ray Brook with symptoms attributable to advanced pulmonary tuberculosis. In addition to the larger mottled shadows on the roentgenograms, numerous punctate abnormal shadows were widely distributed in the lung fields. A diagnosis of silico-tuberculosis was made. Pulmonary heart disease developed and death occurred in July, 1941, approximately three and one-half years after the tuberculosis was discovered (figure 3b).

Autopsy disclosed both silicosis and tuberculosis. Silicosis occurred principally in the discrete nodular form, there being relatively little tendency toward conglomeration. The silicotic nodules evidently constituted local areas of decreased resistance, since virtually all of them were involved in the tuberculous process. In addition, there were numerous, small bronchogenic tuberculous lesions occurring independently of the silicosis.

Case 4: C. H., age 62, came to us in 1936 suffering from moderately advanced pulmonary tuberculosis confined principally to the upper portion of the right lung (figure 4). Tubercle bacilli were present in the sputum. That he had worked for five years as a granite cutter in the Vermont quarries around 1900 (thirty odd years before) was duly recorded but, in view of the short period of dust exposure and the absence of roentgenographic shadows compatible with generalized linear fibrosis or nodulation, a diagnosis of silicosis was not made. The disease progressed steadily in both lungs and was terminated by a fatal hemoptysis in February, 1944.

Autopsy disclosed massive conglomerate silico-tuberculous lesions in both upper lobes and in the right middle lobe. The right upper lobe was the site of a large antrum. Elsewhere there were numerous silicotic nodules measuring from 1 to 7 mm. in diameter. There was no cellular evidence of tuberculosis in or about the discrete nodules but the larger ones contained central areas of necrosis probably due to tuberculosis. As little as three years before death the nodules were not roentgenographically demonstrable. They had definitely increased in size during the time the patient suffered from advancing pulmonary tuberculosis.

DISCUSSION

Inhaled mineral dust, if retained, comes to rest for the most part in and about the lymphatic channels draining the lungs. There it may excite the formation of fibrous tissue, which, if sufficient in amount, is indicated on the roentgenogram by generalized exaggeration of the linear markings. Not only does this particular roentgenographic appearance follow the inhalation of various dusts, it may be simulated by infectious or neoplastic diseases of the lungs and by pulmonary congestion, and therefore cannot be regarded as a specific sign of silicosis.

With most mineral dusts, regardless of dosage, the fibrous tissue reaction does not advance beyond the stage which produces exaggeration of the linear markings on the roentgenogram. By contrast, free silica dust, if inhaled in sufficient quantity, will bring about the formation of wide-spread hyaline fibrous nodules,

the shadows of which constitute the most distinctive roentgenographic sign of silicosis. Sayer and Lanza (1) state that a positive diagnosis of silicosis should not be made unless there is "nodulation throughout both lung fields,"—so important is this sign considered.

By this widely accepted standard none of the 4 cases herein presented was initially considered to have silicosis of clinical importance. In 2 instances silica inhalation by itself was not sufficient to produce any roentgenographically demonstrable generalized fibrosis while in 2 there was merely exaggeration of the linear markings. No doubt there was an appreciable amount of silica dust in the tissues in each instance but not enough pulmonary fibrosis resulted to cast well marked shadows on the roentgenograms. In 3 cases the periods of exposure to silica dust were relatively short, seven, fourteen and five years, respectively, in keeping with the X-ray findings.

The late or even terminal appearance of shadows compatible with generalized nodulation is apparently due to the fact that tuberculosis accelerates the growth and enhances the size of the silicotic nodule. In addition, the development of tuberculous disease about the nodule further contributes to a more conspicuous shadow on the roentgenogram. Certain dust mixtures containing a portion of free silica will not bring about the formation of mature silicotic nodules in experimental animals unless there is associated tuberculosis (2). In human lungs, silicotic nodules tend to be more numerous, larger and more typically hyaline in the vicinity of tuberculous lesions even though the latter appear pathologically inactive.

In middle-aged men with silicosis the development of rapidly progressive tuberculosis suggests that silicosis rendered them more susceptible to the infectious disease. The intimate association of the two conditions observed under the microscope confirms the well known premise that silica dust in the tissues provides a soil peculiarly adapted to the development of tuberculosis. The cases included in this study are typical in these respects despite the initial latency of the silicosis.

It is understandable that a certain amount of tuberculous disease would be likely to develop independently of the silicosis because of the destructive and often ulcerative nature of the lesions. Thus, in the first case, tuberculosis invaded the pleural space; in the second, there were areas of tuberculous pneumonia usually in close proximity to a silico-tuberculous antrum; in the third case, small but widely disseminated bronchogenic tuberculous lesions were found. Moreover, 18 of 24 silico-tuberculous patients coming to autopsy at Ray Brook showed tuberculous lesions even in distant organs which had not been involved in the silicotic process.

A survey of 77 patients coming to Ray Brook with both silicosis and tuberculosis showed that there was no correlation between the size or number of the silicotic nodules determined roentgenographically and the rapidity with which death from tuberculosis occurred. Therefore, the degree of nodulation is not a reliable criterion of susceptibility to tuberculosis even in obvious silicosis.

CONCLUSION

From the evidence presented, we have come to regard with concern a history of even relatively short exposure to silica dust in a tuberculous patient. Silicosis can exert a harmful effect on the patient's resistance to tuberculosis even when generalized pulmonary fibrosis due to silica is so slight that evidence of it is meagre or entirely lacking on technically satisfactory roentgenograms.

CONCLUSIONES

A juzgar por los datos presentados, debe considerarse con seriedad, en todo tuberculoso, una historia hasta de exposición relativamente breve al polvo de sílice. La silicosis puede ejercer un efecto nocivo sobre la resistencia del enfermo a la tuberculosis, aun cuando sea tan leve la fibrosis pulmonar generalizada producida por la sílice, que los signos de la misma sean escasos o falten por completo en roentgenogramas técnicamente satisfactorios.

REFERENCES

(1) Sayer and Lanza: Silicosis and Asbestosis—A. J. Lanza, Oxford University Press, 1938, p. 54.
(2) Sayer and Lanza: Ibid., p. 341.

A MASS CHEST X-RAY SURVEY IN PHILADELPHIA WAR INDUSTRIES[1]

WILLIAM F. ELKIN,[2] MARY A. IRWIN AND CHARLES KURTZHALZ

With the development of the inexpensive small film and paper radiogram, the routine X-ray examination of the chests of apparently healthy persons has been *widely accepted as a practical method of discovering unknown cases of tuberculosis.* The value of such a procedure has been extensively demonstrated by military authorities at induction centres and by the United States Public Health Service in its nation-wide surveys in industry (1).

On October 28, 1942, the Philadelphia Tuberculosis and Health Association, with the coöperation of the United States Public Health Service and the Philadelphia Department of Public Health, began a series of mass X-ray surveys in the industrial plants of Philadelphia. By the end of May, 1945, 169,703 persons had been X-rayed in 47 surveys.

This study is concerned with the findings on 71,767 civilians employed in the Philadelphia Navy Yard, the Frankford Arsenal and the Philadelphia Signal Depot. A particular feature of the survey in these three industries is the fact that X-ray examinations were practically compulsory and resulted in an unusually high percentage of participation by employees. All persons included in the survey were working when X-rayed and had been given a preëmployment physical examination, not including chest X-ray examination.

The survey was conducted under the active supervision of a Committee on X-ray Surveys of the Philadelphia Tuberculosis and Health Association, consisting of W. Edward Chamberlain, M.D., Professor of Radiology, Temple University; David A. Cooper, M.D., then Chief of the Division of Tuberculosis of the Philadelphia Department of Public Health; Esmond R. Long, M.D., Director of the Henry Phipps Institute; and Eugene P. Pendergrass, M.D., Professor of Radiology, University of Pennsylvania.

A photofluorographic unit was employed and a 4" x 5" film was taken of every employee included in this study. All films were processed in the X-ray laboratory at Temple University Hospital. In questionable cases 14" x 17" films were used for checking the interpretation of small films. The findings on all significant cases were forwarded to the medical officer in each establishment. The diagnosis on these cases was completed by a thorough physical examination, including history, sputum test and a 14" x 17" X-ray film. The final check-up was usually done at one of the City Chest Clinics. Nonresidents of the city were given final examinations at the Henry Phipps Institute. A report on all active cases, as required by law, was made by the clinic physician to the Division of Tuberculosis. The follow-up on all cases requiring treatment or supervision was then carried on

[1] From the Philadelphia Tuberculosis and Health Association, Philadelphia, Pennsylvania.

[2] Present address: Oak Ridge Department of Health, Oak Ridge, Tennessee.

in the usual manner through the various chest clinics in coöperation with private physicians. The standards of the National Tuberculosis Association were followed in the diagnosis of cases and classification of findings.

For the practical purposes of this study, findings were divided into three general groups:

I. Reinfection tuberculosis.
II. Other findings.
III. Essentially negative.

This grouping is similar to that used by the Tuberculosis Control Division of the United States Public Health Service (1).

EXTENT OF DISEASE

Attention is called to the fact that this report and the accompanying tables are based entirely on survey film readings. The diagnosis in each individual case was subject to change following the more complete examination by the clinic or private physician to whom the employee was referred.

Table 1 presents the number and per cent of reinfection tuberculosis by extent of disease according to race and sex.

TABLE 1

Number and per cent of reinfection tuberculosis by extent of disease according to race and sex

EXTENT OF DISEASE	WHITE				NON-WHITE				TOTAL	
	Male		Female		Male		Female			
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Minimal	658	68.4	188	74.6	159	74.0	43	75.5	1,048	70.5
Moderately advanced	251	26.1	55	21.8	37	17.2	10	17.5	353	23.8
Far advanced	53	5.5	9	3.6	19	8.8	4	7.0	85	5.7
Extent of disease unspecified[a]	96	—	15	—	26	—	10	—	147	—
Total	1,058		267		241		67		1,633	

[a] Not included in percentage computations.

Of the 71,767 individuals X-rayed, 1,633, or 2.3 per cent, were classified as having X-ray evidence of reinfection tuberculosis. There were 147 cases in which the extent of disease was not specified. Of the remainder, 1,048 (70.5 per cent) were minimal, 353 (23.8 per cent) moderately advanced and 85 (5.7 per cent) far advanced.

As compared with the surveys of the United States Public Health Service, the percentage of total cases found is somewhat higher in the Philadelphia survey, but the proportion of minimal, moderately advanced and far advanced is essentially the same. As of December 31, 1944, the United States Public Health Service

reported 875,909 X-ray examinations made by its units, including those owned by states but operated by officers of the United States Public Health Service. In their surveys it was found that reinfection tuberculosis comprised 1.3 per cent of the total and was made up of 67.7 per cent minimal, 26.9 per cent moderately advanced and 5.4 per cent far advanced (2).

FINDINGS ACCORDING TO RACE

A total of 1,325 cases was found in white persons, which represented 2.4 per cent of the entire white population X-rayed. In the non-white, 1.9 per cent, or 308 persons, were found to have reinfection tuberculosis. The white persons X-rayed constituted 78 per cent of the total number but accounted for 81 per cent of the tuberculosis cases, while non-whites made up 22 per cent of the total number surveyed and accounted for 19 per cent of the cases.

Similar findings were reported in an X-ray study on 65,459 persons, conducted in New York City and reported by Kurzrok and Anderson (3). In that study, 18.6 per cent of those surveyed were white and accounted for 27.4 per cent of the tuberculosis cases found, while Negroes comprised 71.2 per cent of the group X-rayed and produced 62.7 per cent of the cases.

A possible explanation for the disparity between the incidence of tuberculosis uncovered in our X-ray survey of Negro workers in industry and the Philadelphia mortality rate for tuberculosis in Negroes of 192 per 100,000, lies in the more exudative response of the Negro to the tubercle bacillus. He may be too ill when he has active disease to be at work.

INCIDENCE AND EXTENT OF DISEASE BY AGE GROUPS

The distribution of cases by age and according to race and sex is entered in table 2.

The median age of persons found with reinfection tuberculosis was 44 years. The median age of the total number X-rayed was 31 years.

The increment in the incidence of tuberculosis parallels the increase in age. In the white males the percentage of tuberculosis rises consistently from 0.3 per cent in the 15 to 19 year age group, to 9.4 per cent in the age group 65 and over. This higher incidence in the older age group is in keeping with the findings of Edwards (4) and with the death rates in the general male population as computed by Drolet (5). This steady increase in tuberculosis incidence is independent of both sex and race, as is seen in table 2.

A similar increase is also apparent in the white females and the non-white males, although the small number assigned to some of the individual age groups subjects the age trend to greater random fluctuation. Even in the non-white females, an increase with age is obtained when the five-year age groups are combined into larger ones, thus the percentages of tuberculosis in the latter group in the 15 to 24, 25 to 44, and 45 and over age groups are 1.0 per cent, 2.1 per cent and 2.8 per cent, respectively.

Table 3 demonstrates the fact that there was no preponderance of any particular stage of disease in any particular age group.

CARDIOVASCULAR FINDINGS

While the present study was concerned primarily with the incidence of tuberculosis in an industrial population, the findings included a number of other conditions, many of which were of clinical significance. Numerically, cardiovascular conditions were the most important. Some estimate of their prevalence may be

TABLE 2

Reinfection tuberculosis by age according to race and sex

Number examined, number and percentage of reinfection tuberculosis

AGE GROUP	WHITE						NON-WHITE						TOTAL REINFECTION TUBERCULOSIS		
	Male			Female			Male			Female					
	Number Examined	Tuberculosis	Per cent	Number examined	Tuberculosis	Per cent	Number examined	Tuberculosis	Per cent	Number examined	Tuberculosis	Per cent	Number X-rayed	Cases of tuberculosis	Per cent
years															
15–19	3,096	8	0.3	3,691	24	0.7	1,092	16	1.5	444	2	0.5	8,323	50	0.6
20–24	3,905	28	0.7	5,183	45	0.9	1,233	15	1.2	1,133	13	1.1	11,455[a]	101	0.9
25–29	5,574	52	0.9	2,274	34	1.5	1,653	22	1.3	825	16	1.9	10,326	124	1.2
30–34	5,504	96	1.7	1,404	25	1.8	1,828	34	1.9	587	14	2.4	9,324[b]	169	1.8
35–39	4,886	110	2.3	1,240	43	3.5	1,790	37	2.1	415	10	2.4	8,332[c]	200	2.4
40–44	4,629	151	3.3	1,135	28	2.5	1,591	26	1.6	286	5	1.7	7,641	210	2.7
45–49	5,077	219	4.3	886	30	3.4	1,631	43	2.6	158	3	1.9	7,752	295	3.8
50–54	3,456	195	5.6	516	23	4.5	776	26	3.4	70	1	1.4	4,818	245	5.1
55–59	1,768	109	6.2	208	13	6.3	384	14	3.6	18	2	11.1	2,378	138	5.8
60–64	763	58	7.6	63	2	3.2	160	6	3.8	6	1	16.7	992	67	6.8
65 and over	340	32	9.4	20	—	—	62	2	3.2	—	—	—	422	34	8.1
All ages	39,002[d]	1,058	2.7	16,620	267	1.6	12,200	241	2.0	3,942	67	1.7	71,767[d]	1,633	2.3

[a] Includes 1 white, sex unknown.
[b] Includes 1 female, color unknown.
[c] Includes 1 white, sex unknown.
[d] Includes 4 of unknown age.

made from table 4. While these and other abnormalities were reported to the medical officers at the industrial plants, the Tuberculosis Association was not in a position to follow through in the same manner as was done with tuberculosis, and table 4 represents the gross reading of films as they were found incidental to the search for tuberculosis.

TABLE 3

Number and per cent of reinfection tuberculosis by age according to extent of disease

AGE GROUP	NUMBER EXAMINED	MINIMAL TUBERCULOSIS		MODERATELY ADVANCED TUBERCULOSIS		FAR ADVANCED TUBERCULOSIS		TOTAL REINFECTION TUBERCULOSIS[b]	
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
years									
15–19	8,323	29	0.3	9	0.1	2	0.0	50	0.6
20–24	11,455	67	0.6	19	0.2	7	0.1	101	0.9
25–29	10,326	78	0.8	24	0.2	9	0.1	124	1.2
30–34	9,324	113	1.2	33	0.4	5	0.1	169	1.8
35–39	8,332	129	1.5	39	0.5	12	0.1	200	2.4
40–44	7,641	141	1.8	41	0.5	11	0.1	210	2.7
45–49	7,752	181	2.3	73	0.9	12	0.2	295	3.8
50–54	4,818	157	3.3	56	1.2	11	0.2	425	5.1
55–59	2,378	91	3.8	29	1.2	9	0.4	138	5.8
60–64	992	42	4.2	19	1.9	5	0.5	67	6.8
65 and over	422	20	4.7	11	2.6	2	0.5	34	8.1
All ages	71,767[a]	1,048	1.5	353	0.5	85	0.1	1,633	2.3

[a] Includes 4 of unknown age.
[b] Includes reinfection tuberculosis with extent of disease unspecified.

TABLE 4

Cardiovascular findings of presumed significance in 71,767 persons X-rayed

POSITIVE FINDING OR INTERPRETATION	NUMBER FOUND	PER CENT OF THOSE X-RAYED
Widened aorta[a]	644	0.9
Aneurysm	83	0.1
Heart disease as evidenced by alteration in size or shape of heart shadow	598	0.8
Miscellaneous other	84	0.1
Total	1,409	2.0

[a] It is obvious that single ventral projections, as used in tuberculosis case finding surveys, regardless of size of film, are incapable of differentiating, for example, between significant and nonsignificant widening of the aortic shadow. A "wide aortic shadow" may be produced by a normal aorta due to tortuosity.

SUMMARY

The X-ray findings in a survey of 71,767 civilians employed in three large military industrial plants in Philadelphia are presented.

A total of 1,633 persons (2.3 per cent) bore X-ray evidence of damage to the lungs by reinfection tuberculosis. There were 147 cases in which the extent of the disease was not specified. Of the remaining 1,486, 1,048 (70.5 per cent) were minimal, 353 (23.8 per cent) moderately advanced and 85 (5.7 per cent) far advanced.

A total of 1,325 cases was found in white individuals, which represented 2.4 per cent of the white population X-rayed. In the non-white, 1.9 per cent, or 308 cases were found.

The prevalence of tuberculosis increases with age. In white males the percentage of tuberculosis rises consistently from 0.3 per cent in the 15 to 19 year age group to 9.4 per cent in the age group 65 and over. This steady increase in tuberculosis prevalence is not confined to white males; it was noted also in colored males, and in females, both white and colored.

Cardiovascular abnormalities found incidental to the search for tuberculosis numbered 1,409, or 2.0 per cent of those X-rayed.

SUMARIO

En un estudio roentgenológico de 71,767 paisanos empleados en tres grandes fábricas de productos militares en Filadelfia, 1,633 (2.3%) mostraron signos roentgenológicos de lesiones pulmonares producidas por tuberculosis tipo reinfección. En 147 casos no se mencionó la extensión de la enfermedad; de los otros 1,486, 1,048 (70.5%) eran mínimos, 353 (23.8%) moderadamente avanzados y 85 (5.7%) muy avanzados.

Un total de 1,325 casos correspondió a sujetos blancos que representaban 2.4% de la población blanca radiografiada. Entre las otras razas se descubrieron 308 casos (1.9%).

La frecuencia de la tuberculosis aumenta con la edad. En los varones blancos el porcentaje de tuberculosis se eleva constantemente: de 0.3% en el grupo de 15 a 19 años de edad a 9.4% en el grupo de 65 años y más de edad. Este aumento constante no se limita a los varones blancos, pues se observa también en los negros y en las mujeres de ambas razas.

Las anomalías cardiovasculares descubiertas fortuitamente en la pesquisa de la tuberculosis ascendieron a 1,409: 2% de los radiografiados.

REFERENCES

(1) Hilleboe, Herman E., and Morgan, Russell H.: Mass Radiography of the Chest, Chicago, The Year Book Publishers, 1945.
(2) Van der Vate, Jan: Personal communication, March 21, 1945.
(3) Kurzrok, Milton, and Anderson, Peyton: Am. Rev. Tuberc., 1940, *41*, 89.
(4) Edwards, Herbert R.: Supplement to Am. Rev. Tuberc., June, 1940.
(5) Drolet, Godias J.: Present trend of case fatality rates in tuberculosis, Am. Rev. Tuberc., 1938, *37*, 125.

TUBERCULIN PPD

A Single Intermediate Dosage Used in Surveying 8,000 Persons

FRANCISCO J. MENENDEZ[1]

In August, 1939 we began the systematic study of the tuberculin reactions among all those attending the Laennec Dispensary, extending the study especially to those living in the same household with tuberculous persons and to those who came for examination through the efforts of the visiting nurses.

In this manner we are carrying on a "Tuberculin-Clinical-Radiological Survey" which has certain characteristics different from the large "Depistage Surveys." It is usually the practice in those surveys to examine by X-ray only those persons who react to tuberculin, while in our study all persons, positive as well as negative, are systematically examined, including a clinical-radiological examination, sputum examination, blood examination, etc. On the other hand, almost all those examined are well persons with respiratory symptoms, this being the reason for which they came to the Dispensary for examination. The majority belong to the poorest class and live under bad hygienic-social conditions. It is therefore not surprising that the rate of infection and of illness is higher than that found in other surveys carried on in our country.

We used PPD tuberculin obtained by the Florence B. Seibert method, approved and adopted by the Committee on Medical Research of the National Tuberculosis Association.

We began this survey following the recommended technique which consists in the use of two doses of different strengths. Those who did not react to the first injection with the weak dose were given the second test with a stronger dose forty-eight hours later. After having examined more than 2,000 persons with this technique, our attention was called to the fact that a large number of persons failed to agree to the reading of the test. Investigating the possible causes of this situation, we found that one of the reasons was based on the fact that, of the 75 per cent of the cases which did not react to the first test, many did not return for the reading of the second test in spite of all our efforts. We tried to obviate this difficulty by the use of a single medium dose which would fill all the needs and comply with all the requisites of the recommended technique of two doses; that is, it was sufficiently strong for discovering the greatest possible number of tuberculin-positive cases and, at the same time, it would not produce a high percentage of serious reactions, cutaneous or otherwise.

After testing and comparing different dilutions, we adopted as the single medium dose a dilution four times weaker than the dose used for the second test in the recommended technique, or 0.001,25 mg. of PPD (which corresponds to 0.65 mg. of OT).

We have made a comparative study of the value of the single medium dose

[1] Perseverancia 164, Havana, Cuba.

with the "recommended technique" of two doses in two series of cases. In the first group of 2,610 cases we used the recommended technique of two doses—a first weak dose (0.000,02 mg. of PPD) and a second stronger dose (0.005 mg. of PPD). In the second group we examined 5,390 cases using the single medium dose (0.001,25 mg. of PPD).

In the first group (2,610 cases) in which we used two doses of different strengths, in 675 cases, or 25.86 per cent, there was no agreement to the reading of the test. In the second group (5,390 cases) in which a single medium dose was used, there were only 765 cases, or 14.20 per cent, without verification. In other words, the number of cases lost by failure of agreement to the reading of the test is reduced to a minimum.

Deducting the cases lost in each of the two groups, there remained for study 6,560 persons in whom there was agreement to the reading of the test, and they were given clinical, X-ray and laboratory examinations, divided as follows: group I (1,935 cases) in which the recommended technique of two doses was used; group II (4,625 cases) in which we used the single medium dose.

Making these two groups the basis of our comparative study of the results obtained with both techniques, we found that the percentage of tuberculin reactors is a little more in group I (recommended technique), namely, 76.85 per cent; while in group II (the single medium dose) the percentage of reactors was 73.40. This small difference, which in our judgment does not invalidate the advantages which we feel the single medium dose has, can be easily eliminated by retesting with the stronger dose those not reacting to the medium dose.

With regard to the intensity of the cutaneous reactions in the tuberculin reactors, the percentages were similar in the two groups, as can be seen in the following tabulation.

We especially wish to point out that in the four-plus reactions very little difference was observed in both groups.

	RECOMMENDED TECHNIQUE				SINGLE MEDIUM DOSE	
	First dose	Second dose	Total	Per cent	Total	Per cent
+	416	349	765	39.58	1,744	37.71
++	89	247	336	17.36	832	17.99
+++	26	234	260	13.43	403	8.72
++++	11	115	126	6.51	415	8.89
Total reactors			1,487	76.85	3,394	73.40
Total nonreactors			448	23.15	1,231	26.60

Another interesting aspect of the single medium dose is the economy. As only one dose is used, and this is four times weaker than that used in the second strength, it represents a great economy in the cost of the tuberculin required. Comparing the total number of tests given in the two groups of our survey, the difference in cost of the two techniques can be seen.

First series (recommended technique)—2,610 cases

Negative to first and second doses	448 cases,	982 tests
Positive to first dose	542 cases,	542 tests
Positive to second dose	945 cases,	1,890 tests
Without confirming first dose	444 cases,	444 tests
Without confirming first and second doses	231 cases,	462 tests

Total tests given, 4,320 Cost, $76.10

Second series (single medium dose)—5,390 cases

Total tests given, 5,390 Cost, $24.25

As one can see the single medium dose is 84 per cent more economical than the recommended technique of two doses of different strengths, or, in other words, the per capita cost of the tuberculin test was $0.03 in the first group and $0.005 in the second group, which in the large "Depistage Surveys" represents a considerable saving.

Regarding the use of the PPD solution, we do not believe it necessary for it to be freshly prepared, since we have been able to prove experimentally the same results in the same group of cases by using solutions recently prepared and that conserved for seven weeks in the refrigerator, always taking the necesssary aseptic precautions in the preparation of these solutions.

Following is a brief résumé of the results obtained up to the present time in this survey.

In the 6,560 cases in which agreement in the reading of the tuberculin test existed, 4,881 were positive, or 74.5 per cent, a figure which does not represent the rate of infection of the Cuban population, since, as we have said before, the total number of cases examined comprised persons with respiratory symptoms, living with tuberculous persons, who belonged to the poor class, the majority of whom live under bad hygienic-social conditions.

In this group of 6,560 cases there were 1,574 with manifest tuberculosis, which represents a morbidity rate of 24 per cent. By dividing this group into reactors and nonreactors to the tuberculin test, the following results were obtained:

	NUMBER OF CASES	WITHOUT LESIONS	WITH LESIONS	RATE OF MORBIDITY
				per cent
Nonreactors	1,679	1,365	314	18.69
Reactors	4,881	3,621	1,260	25.81

It is of interest to note that, among the nonreactors to the two doses of tuberculin used, 18.69 per cent of the cases showed tuberculous lesions which proves that it is not satisfactory to X-ray only the reactors, as is done in the large "Depistage Surveys," because there exists a high percentage of illness among the group of nonreactors.

CONCLUSIONS

1. With the use of the single medium dose, the number of cases lost by lack of agreement to the reading of the test is reduced to about one-half.
2. The percentage of tuberculin reactors is practically the sáme using either technique.
3. A marked relationship exists in the percentage of intensity of the cutaneous reactions obtained with either technique.
4. The single medium dose represents a great economy in time and money in the systematic application of the tuberculin test.
5. The solutions of PPD preserved in the refrigerator conserve their strength for seven weeks.
6. In the "Depistage Surveys" in which only the reactors are X-rayed, it is necessary to take into account the nonreactors among whom many cases of tuberculosis exist.

CONCLUSIONES

1. Con el empleo de la "dosis media unica," el numero de casos per didos por no concurrir a la lectura de la prueba se reduce practicamente a la mitad.
2. El porcentage de tuberculino-reacciones positivas es practicamente igual con ambas tecnicas.
3. Existe un marcado paralelismo en el porcentage e intensidad de las reacciones cutaneas obtenidas con ambas tecnicas.
4. La dosis media unica representa una gran economia de tiempo y dinero, en la practica sistematica de la tuberculino-reacción.
5. Las soluciones de tuberculina P. P. D. guardadas en el refrigerador conservan su potencia durante 7 semanas.
6. En los Surveys de Depistage no basta con practicar el exámen radiologico solo de los tuberculino-positivos, pues es necesario tener en cuenta que entre los no reactores existen muchos casos con tuberculosis enfermedad, que de esta suerte se escaparian al control.

PULMONARY LAVAGE

A Method for Demonstrating Tubercle Bacilli

MANOEL DE ABREU[1]

The bacteriological examination is of the utmost importance in the diagnosis of active pulmonary tuberculosis. The presence of the bacillus really separates diseased persons from those who are not. Bacteriological studies are indispensable in the planning of any social or prophylactic measures. The systematic and periodical examination by means of fluorography, discovering bearers of shadows in the lungs, frequently during the initial period of tuberculosis, has come to prove that bacteriological examination according to customary techniques is not entirely satisfactory.. A large number of problems appear with serious consequences. Are we dealing with progressive or residual tuberculosis? Should we give pneumothorax or should we wait? In the case of an employee or laborer should he be admitted, be given leave of absence, pensioned off? Should a health certificate be granted or not? The presence or absence of the bacillus in the sputum constitutes thus the indispensable complement to the radiographical examination, without which there can be no etiological-pathological diagnosis.

In order to resolve such a distressing problem, phthisiologists are resorting to the examination of the sputum and gastric lavage. The former requires the presence of sputum in sufficient quality and quantity and is, therefore, useful mostly in cases of progressive pulmonary tuberculosis, often with cavities. Gastric lavage is not always reliable and, in patients with active tuberculosis, may be repeatedly negative. Indeed, the presence of broncho-alveolar secretion in the fasting stomach varies in proportion to several factors which render the above mentioned examination deficient and laborious.

With these considerations in mind, and participating in a Diagnosis Revision Committee which handles numerous cases, which demand a rapid and accurate diagnosis, we thought of using a new technique, the pulmonary lavage or tracheobronchoalveolar lavage, which seems to us to be the solution to the problem of demonstrating tubercle bacilli.

TECHNIQUE OF THE LUNG LAVAGE

We give below the two techniques of pulmonary lavage:

First Technique:

1. Anesthesia of the tonsillar plicae, uvula and pharynx, using 1 to 2 cc. of a 0.5 per cent solution of novotutocain. The anesthesia should be applied slowly with a small syringe of 2 cc. capacity. Stovaine in 2 per cent solution sometimes gives good results. The anesthetic solution must be prepared just before its application or preserved in closed ampoules.
2. Wait three or four minutes until the patient demonstrates sensations peculiar to the action of the anesthetic.

[1] Rio de Janeiro, Brazil.

3. Slight traction and fixation of the tongue with the hand, protected by a gauze dressing. Anesthesia of the pharynx, larynx and tracheobronchial channel during inhalation (1 to 2 cc. of the same 0.5 per cent solution of novotutocain). Proceed slowly, while the patient inhales.
4. Provoke cough and collect secretion or material for examination. This collection should be made from the beginning of the experiment.

Second Technique:

1, 2 and 3 have already been explained above.

4. Wait for about five minutes in order to verify the effect of the anesthetic, using the smallest possible dose of novotutocain.
5. Inject, under the same conditions, from 5 to 10 cc. of physiological saline solution during inhalation.
6. Provoke cough and collect secretion or material for examination.

We advise previous cleansing of the mouth and the removal of false teeth, dental plates, etc. The phase of collection of the secretion should also be prolonged, so as to obtain abundant material.

The patient should be in a fasting condition, even remaining so up to two hours after the experiment, because of the effect of the anesthetic.

We are convinced that the technique of pulmonary lavage has become a simple operation to obtain tracheobronchial secretion. In the last lavages we used only exceptionally 10 cc. of saline following application of the anesthetic. In most cases, the first two steps of the anesthesia process, with 4 cc. of 0.5 per cent novotutocain, have enabled us to obtain secretion in sufficient quantity for bacteriological examination. In this case, the collection of the material should take place during anesthesia and should be carried out as long as required. Such a technique, in which the minimum quantity of liquid is aspirated, seems satisfactory, rendering the method not dangerous, even in cases of chronic pulmonary diseases.

The second technique is only used when simple anesthesia does not produce the desired effects, in cases with slight lesions without spontaneous expectoration.

ACTIVE AND INACTIVE TUBERCULOSIS

The aim of the Diagnosis Revision Committee is to ascertain as quickly as possible in which classification the patient belongs according to the following classification:

Nontuberculous disease.
Inactive tuberculosis.
Active tuberculosis.

In the case of a nontuberculous disease, a diagnosis should be arrived at and this has been done in several instances (emphysema, air cysts, congenital bronchiectasis, other pulmonary diseases, cardiovascular disease, etc.).

The activity or progressive potentiality of tuberculous lesions is reflected in the symptomatology, in radiographic findings and in bacteriological data. The latter seem to us to be the most important, especially if the material collected by

lavage is cultured and inoculated into guinea pigs. We have observed perfect agreement between radiography and bacteriology. In only 3 cases did the radiographic shadow appear relatively large while the bacteriological findings were negative. Such apparent disagreement should be cleared up by prolonged observation of the patients, who may have closed tuberculosis or nontuberculous diseases, such as blastomycosis. Cases with a tomographic diagnosis of a cavity, which sometimes has a small diameter, have revealed positive lavages. One case of primary tuberculosis in an adult (primary complex and erythema nodosum) revealed a positive lavage.

Generally speaking, the fibrous forms, accompanied by calcification, were negative on bacteriological examination. On the contrary, exudative and excavated forms were positive.

Only once has a lavage of the lung been repeated, in the case of a discrepancy between radiographic and bacteriological findings. The second test confirmed the first. No bacilli were found.

Another important point is the following: the majority of the positive cultures presented few colonies, sometimes one or two in five tubes, for it concerned paucibacillary patients with several previous negative examinations. The aforesaid circumstance demonstrates the efficiency of pulmonary lavage, followed by a thorough bacteriological test.

BACTERIOLOGY

Direct examination, culture on Loewenstein's medium and guinea pig inoculation are systematically made. Culture and inoculation are indispensable, especially in forms of tuberculosis without sputum or with a negative one. In 32 positive lavages, the positive findings were obtained by the following techniques:

Direct examination	5–15.6 per cent
Culture	22–68.8 per cent
Inoculation	5–15.6 per cent
Total	32

Thus, direct examination without digestion was positive five times. In about 70 per cent of the cases culture revealed the presence of bacilli, usually with a few colonies in each tube. Lastly, in approximately 16 per cent of the lavages, only inoculation proved decisive.

In the 32 cases of positive examination, innumerous negative tests had been made in the usual manner, including gastric lavage.

STATISTICS

Until now, 450 lung lavages have been performed, of which 313 are complete. In the rest, the time necessary for obtaining the results of cultures and guinea pig inoculations has not elapsed.

These first statistics reveal the following results: Pulmonary lavage in patients without sputum or with negative sputum (313 original cases):

	Number	Negative	Positive
Suspected	176	160	16— 9.1 per cent
Patients and ex-patients	137	105	32—23.4 per cent
Total	313	265	48—15.4 per cent

In our first 42 lavages we had 33.3 per cent positive findings; in the last 38, however, this was reduced to 7.9 per cent. The presence of the bacillus depends on the human material, being more frequent in patients under treatment or clinically cured, but rarer in suspected persons who are bearers of discrete shadows, revealed by systematic radiographic examination.

A comparative study between pulmonary and gastric lavage is being made. Dr. R. Fernandes made the two tests on the same day on 18 apparently cured patients, at the Miguel Pereira Hospital. Here are the results:

	Stomach	Lung
Negative	17	10
Positive	1—5.6 per cent	8—44.4 per cent

We emphasize the following fact: the patients appeared to be clinically cured and, in addition, the gastric lavages were performed with exacting skill, that is, after previous hospitalization.

CONCLUSIONS

Pulmonary lavage is yet at the beginning of its application. It is a new method which needs long observation to determine definitely its harmlessness and effiiciency. At this stage it is possible to state that the supra- or trans-glottic way offers no danger (450 cases), although it should be performed with the utmost exactitude by using efficient anesthetics in the smallest possible doses. In accordance with our data, it seems to us that pulmonary lavage surpasses in efficiency that of the stomach, being also easier to perform. The negative results correspond radiographically to fibrocalcareous and fibrous lesions; the positive, to exudative, fibro-exudative and cavitary lesions. We are, at the present moment, making a revision of the radiographic interpretation, in the light of the information from tomography and pulmonary lavage. There is no doubt that the new method, by determining more precisely the presence or absence of the bacillus, has, in a measure hitherto unknown, contributed to the diagnosis of active, open and contagious tuberculosis, which is indispensable to treatment, prophylaxis and social or administrative measures.

CONCLUSIONES

El lavado pulmonar encuéntrase todavía en sus comienzos, representando una nueva técnica que exige observación prolongada a fin de determinar definitivamente su inocuidad y eficacia. En esta etapa ya se puede declarar que la vía supra- o trans-glótica no entraña peligro (450 casos), aunque la intervención debe ser ejecutada con la mayor precisión y utilizando anestéticos eficaces a las menores dosis posibles. Según los datos disponibles, el lavado pulmonar supera aparentemente al gástrico en eficacia, siendo además más fácil de ejecutar.

Radiográficamente, los resultados negativos corresponden a lesiones fibro-calcáreas y fibrosas; los positivos, a exudativas, fibro-exudativas y cavitarias. A la luz de los datos aportados por la tomografía y el lavado pulmonar, la interpretación radiográfica se halla ahora en vías de revisión. No cabe duda de que el nuevo método, por determinar con mayor precisión la presencia o ausencia del bacilo, ha contribuído, en un grado desconocido todavía, al diagnóstico de la tuberculosis activa, abierta y contagiosa, lo que es indispensable para el tratamiento, la profilaxis y las providencias sociales o administrativas que estén indicadas.

We are indebted to our colleagues F. Magarão, J. Dauster, R. Fernandes, G. Ribeiro and Machado Junior for their invaluable collaboration in this work.

COMBINATION EGG MEDIA FOR THE DIAGNOSTIC CULTURE OF TUBERCLE BACILLI[1,2]

H. J. CORPER AND MAURICE L. COHN

Two decades after the initial quantitative studies of the value of nutrients for tubercle bacilli (1), it is being conceded that cultural methods are equal to animal (guinea pig) inoculation for the diagnostic disclosure of small numbers of tubercle bacilli, and that the economical as well as practical culture methods possess a number of decided advantages over animal inoculation tests (2). Cultural methods have replaced animal tests in many health department, sanatorium and private laboratories. The use of this delicate diagnostic method has been extended considerably so that the clinician depends upon this valuable means to determine more accurately whether his patients are negative in so far as expelling tubercle bacilli is concerned.

Cultural methods in the past have proved highly efficient; but, since there is no perfect biological method or test, perfection could hardly be expected. Improvements and simplifications are still possible, particularly along the line of the critical experiences of the past. Ever since the earliest attempts to develop diagnostic culture methods for the isolation of tubercle bacilli, it was recognized that this procedure depended upon certain definite and individual parts which bore careful and separate evaluation as well as combined consideration. For the sake of arbitrary convenience, therefore, diagnostic culture methods depend upon several involved individual features and their subordinate parts to attain the requirements prescribed for a perfect method. Primary in the consideration of these divisions or factors would appear to be the choice of a simple and efficient nutrient and, subordinate to this, would be a consideration of any factors either reënforcing or interfering with the nutrients.

In previous communications (3) it was pointed out that potato and egg proved to be entirely adequate nutrients, as tested by quantitative planting methods, and that the yolk possessed certain superiority over the white especially and the whole egg as well. This has now been verified adequately by other observers (4, 5), and in comparative tests it was shown that the addition of numerous other ingredients added nothing to the high efficiency of an appropriately prepared egg-yolk medium. In 1915 Petroff (6), who pioneered in the field of diagnostic culture methods, suggested the addition of gentian violet to an egg medium to retard the growth of such contaminating microörganisms which had escaped his preliminary sodium hydroxide treatment; but the concentration of dye used also retarded the development of small plantings of tubercle bacilli and has accordingly been omitted from most media, including potato media, prepared since then. During this period when the search for retardants was considered important, malachite green also became popular for its retarding action on contaminants and its attractive color which was, however, decolorized

[1] From the Research Department, National Jewish Hospital, Denver, Colorado.

[2] This investigation was aided by a gift from Mr. and Mrs. Lothair S. Kohnstamm.

(reduced) by the growth of the tubercle bacilli in egg media. In Petragnani's medium, a complex mixture, and in Hohn's medium, also a mixture, malachite green attracted attention both as color and retardant. However, later Loewenstein used another attractive color, congo red, without retarding effect upon either contaminants or tubercle bacilli nor did this dye become decolorized. Thus certain students preferred either to omit dyes or to choose them mainly for color value and with equally good results. The stress then was placed on the use of complex mixture media which had not been submitted to scientific evaluation. This evaluation was done in 1942 (7) with the result that a simple egg-yolk medium described in 1933 (3) was found equal in efficiency to any multiple mixture medium thus far described for growing small numbers of mammalian tubercle bacilli. At that time, it was noted that the addition of potato contributed nothing to the efficiency of the egg media but may only yield more voluminous and elevated final colony growth. However, Ordway, Medlar and Sasano (8), who had previously been partial to the guinea pig, saw decided value in the culture and, in 1943 (9), described their egg-yolk-potato medium. It consisted of ground Irish potatoes (200 g.), glycerol (60 cc.), citric acid (0.2 g.), distilled water (1,000 cc.), to which was added guinea pig blood powder (from blood clots), egg-yolk and malachite green. Sterilization as prescribed by them seemed inadequate since the mixture was kept at 90°C. for one hour only, but this satisfied their test. Although still maintaining that "the egg-yolk-potato medium closely approximates, but does not quite equal, the guinea pig test," they state that "The difference we have found is not sufficient to further warrant the use of guinea pigs in a routine diagnostic service, from the standpoint of economy alone."

In 1942 McCarter and Kanne (5) favored egg-yolk media over whole egg media for the isolation of human and bovine tubercle bacilli. In 1944 Powelson and McCarter (10) felt that Hohn's medium with buffer salts, asparagin, beaten whole eggs and 2 per cent aqueous solution of malachite green oxalate was preferable to plain egg-yolk medium, with or without malachite green, because the good nutrient qualities of the latter encouraged growth of contaminants. However, their result might question the efficiency of the sterilization procedure used for their egg-yolk medium.

Now in the second important division, diagnostic culture for tubercle bacilli, that of the preliminary destruction of contaminating microörganisms in the pathological specimen, many reagents have been tried. Four have survived, including sodium hydroxide (3 or 4 per cent), sulphuric acid (6 per cent), hydrochloric acid (3 per cent), and finally 5 per cent oxalic acid which can be prepared from chemically pure and stable crystals, while all the foregoing reagents are more or less unsuited because of the uncertainty of chemical concentration and the difficulty of preparation. Yet it must be recognized that not one of these reagents has yet achieved the perfection of always destroying all contaminants satisfactorily without injury to the desired growth of tubercle bacilli. Further work on this is one of the problems still open for future study. However, it is not to be inferred that reliable results cannot be obtained from the careful and

proper use of any of these reagents. Their use requires caution and intelligence in procedure for best results. Therefore, it is advisable to use at least three and preferably five separate tube plantings to insure optimum and satisfactory findings with individual specimens so that the failure of any one or two tubes may not lead to complete failure of the test.

In a recent meeting of the Committee on Evaluation of Laboratory Procedures of the American Trudeau Society, held in Chicago, February 2, 1945, a number of important problems concerning the value and methods of diagnostic culture for isolating mammalian tubercle bacilli were discussed. At the suggestion of Dr. C. Eugene Woodruff, Chairman, a formula for a combined egg-yolk and potato medium was prescribed by Dr. E. R. Medlar in consultation with the rest of the Committee to find out whether the addition of the potato to the yolk contributed anything to the efficiency of the diagnostic medium. In addition, the Committee members were to study the matter of dye or contrast staining of the medium, which is to be reported on subsequently, in order to make early growth more readily discernible. The potato-egg-yolk medium suggested by Doctor Medlar and the Committee for test was as follows, while a plain yolk medium was to be used for comparison: potato, 100 g.; glycerol, 30 cc.; distilled water, 500 cc.; and egg-yolk, 500 cc. (March 29, 1945, brief report from C. Eugene Woodruff, M.D., Chairman). "The question of whether a dye can be added to the medium without inhibiting growth of tubercle bacilli is to be investigated by members of the Committee, also the possibility of obtaining a non-bacteriostatic *black* dye."

With the directives of the Committee as guide, the following tests were performed. The egg-yolk-potato medium was prepared: 100 g. of grated potatoes were so handled in expedited fashion to avoid detrimental air effects and browning and were mixed with 30 cc. pure glycerol and 500 cc. distilled water; the potato mixture was autoclaved at 15 lbs. pressure for thirty minutes and, after cooling, was mixed with 500 cc. of fresh egg-yolk. The mixture was then carefully tubed, slanted, and sterilized by appropriate autoclaving for twenty minutes at 15 lbs. pressure, using necessary precautions to avoid bubbling of the medium and sterilizer air pockets. For comparison, simply prepared 3 per cent glycerol-egg-yolk medium was used, first described in 1933 (3). Graded planting tests were performed, using five laboratory strains of human and bovine (eugonic) tubercle bacilli and four recently isolated human sputum strains. The use of natural sputum or pathological specimens is never of value for accurate evaluation of the nutrient value of a medium for growing small numbers of tubercle bacilli, since they are composed of irregularly distributed material, varying from planting sample to sample sufficiently to vitiate comparison. The results of these studies with the egg-yolk medium and the yolk-potato medium are recorded in table 1.

The results recorded in table 1 do not justify the conclusion that a medium consisting of a mixture of potato and egg-yolk is superior to a medium consisting of egg-yolk without potato in so far as early growth or number of positive cultures is concerned. Actually, there appeared to be a retardation of the growth

in time of appearance in the yolk-potato mixture as compared with the yolk medium alone. This, however, was of no practical import and therefore resolved itself into a question of simplicity of preparation, which made the egg-yolk medium the logical choice. Since the addition of potato is more liable to improper preparation as far as age, deterioration, etc. is concerned, which led to

TABLE 1

Comparison of simple egg-yolk with egg-yolk-potato medium for the diagnostic culture of mammalian tubercle bacilli

STRAIN	MEDIUM	AMOUNT OF TUBERCLE BACILLI IN MILLIGRAMS (PER CUBIC CENTIMETER) IN SUSPENSION USED FOR PLANTING CULTURE TUBES			
		10^{-2}	10^{-4}	10^{-6}	10^{-8}
"Avirulent human"	Yolk	2†	2	3	3^{2}
	Yolk and potato	2	2	3	4^{1}
4008	Yolk	2	3	4	5
	Yolk and potato	3	3	4	6
H37 RV	Yolk	2	2	3	3
	Yolk and potato	2	3	3	4
Gluckson	Yolk	2	2	3	3
	Yolk and potato	2	2	3	3^{2}
Bovine virulent	Yolk	2	2	3	3
	Yolk and potato	2	2	3	3
3145*	Yolk	2	4	4	0
	Yolk and potato	3	4	4	0
4105*	Yolk	2	2	4	0
	Yolk and potato	3	3	4	0
4265*	Yolk	2	2	3	4^{2}
	Yolk and potato	2	2	3	4^{2}
535*	Yolk	2	2	3	6^{1}
	Yolk and potato	2	2	3	6^{2}

* Original sputum isolations.

† The numeral indicates the number of weeks' incubation after which the culture became positive. When all 3 tubes are positive, no exponent is used; exponent 1 and 2 indicate one or two tubes positive.

its lack of popularity previously, it would seem well to avoid such difficulties by a more stable and reliable basic substance such as the fresh egg-yolk. Egg-yolk does not show alteration when exposed to air or like natural influences readily affecting the composition of the potato and disturbing its nutrient value for tubercle bacilli.

In 1942 (7) it was reported that Petragnani's medium was not superior to the egg-yolk medium, but no particular attention was paid to the dye, malachite green, used in this medium. It appeared that malachite green was the attraction which encouraged technicians to adhere to this medium for diagnostic cultures of mammalian tubercle bacilli. Just what attraction malachite green could be was not certain; but, for further elucidation, it seemed desirable to try Petragnani's medium again and compare it with a simple yolk medium containing malachite green in various concentrations. Thus it would be possible to place a better interpretation both on the media and the dye, which latter was credited with retardant action against contaminants. The Petragnani medium (differing slightly from that used previously (7)) consisted of potato 75 g., milk (cream removed) 150 cc., potato flour 6 g., and peptone 10 g. The foregoing was mixed and heated in a double boiler for ten minutes with frequent stirring. After the mixture became pasty, heating was continued for one hour. Sterile distilled water was added to make to desired volume. The mixture was cooled to 50° C., and to this was added a mixture of 4 whole eggs and the yolk of one egg, glycerol 12 cc., and 10 cc. of a 2 per cent aqueous solution of malachite green. A standard Coleman and Bell dye, certified for biological use with 96 per cent dye content, was used in these preparations. The foregoing medium contained approximately 0.04 per cent malachite green, and on this basis the tabulated percentages are given comparatively. The cultural studies were made with three strains of mammalian tubercle bacilli, two human strains and one bovine. Plantings were carried from 0.01 to 0.000,000,01 mg. of fine suspension. The findings for the human strain 4008 are recorded briefly in table 2, which is essentially the same as for both human strains tested; and table 3 for a eugonic virulent bovine strain of tubercle bacilli.

The findings recorded in table 2 indicate that the yolk medium as compared with the Petragnani medium containing 0.04 per cent malachite green possesses a slight advantage in ability to support the growth of small plantings of human tubercle bacilli, probably because of a slight retarding effect of the malachite green in the concentration (0.04 per cent) recommended for coloring Petragnani's medium. This conclusion is borne out by the further findings recorded in table 2, in which it is noted that increasing concentrations of malachite green, from 0.01 to 0.1 per cent, added to the yolk medium or the Petragnani mixture tend to retard growth as compared with the plain yolk medium. This same conclusion is borne out by a careful study of colony formation on the malachite green media in which it is noted that the dye tends to retard colony spread with the result that there is a tendency to individual colony formation on the malachite green media which may at times lead to the deception of a better growth rather than the limitation exerted by the dye on spread of growth.

In table 3 the findings recorded for the human tubercle bacilli are essentially duplicated with the virulent eugonic strain of bovine tubercle bacilli tested—a retardation in the small plantings of the dye-containing media as compared with the plain yolk media. The dye retardation does not appear to be absolute in the concentrations up to 0.1 per cent although becoming more evident at 0.2 per cent.

TABLE 2

Comparison of yolk-glycerol-water medium and Petragnani's medium and effect of malachite green on growth of virulent human tubercle bacilli

MEDIUM	PER CENT MALACHITE GREEN	AMOUNT OF TUBERCLE BACILLI (4008*) IN MILLIGRAMS (PER CUBIC CENTIMETER) IN SUSPENSIONS USED FOR PLANTING CULTURE TUBES			
		10^{-2}	10^{-4}	10^{-6}	10^{-8}
Yolk	0	2†	3	3	4^{2}
	0.01	2	3	4	7^{1}
	0.02	2	3	4	0
	0.04	3	3	4	8^{1}
	0.06	3	4	5^{2}	0
	0.08	3	4	5	0
	0.1	4	4	6^{2}	0
Petragnani	0.01	2	3	3	0
	0.02	2	3	4	0
	0.04‡	2	3	4	0
	0.06	2	3	4	0
	0.08	3	3	4	0
	0.1	2	3	4	0

* Only the results with human strain 4008 are recorded since essentially the same findings were attained with the other human strain used.

† The numeral indicates the number of weeks when growth first appeared. An exponent (1 or 2) designates the number of positive tubes; no exponent = all three tubes positive.

‡ This is the approximate concentration of malachite green used by Petragnani.

TABLE 3

Comparison of yolk medium and Petragnani's malachite green medium on the growth of virulent bovine (eugonic) tubercle bacilli

MEDIUM	PER CENT MALACHITE GREEN	AMOUNT OF TUBERCLE BACILLI (VIRULENT BOVINE) IN MILLIGRAMS (PER CUBIC CENTIMETER) IN SUSPENSIONS USED FOR PLANTING CULTURE TUBES			
		10^{-2}	10^{-4}	10^{-6}	10^{-8}
Yolk	0	2*	2	3	5^{1}
	0.01	2	2	3	4^{2}
	0.02	2	2	3	0
	0.04	2	2	3	5^{2}
	0.06	2	2	3	3^{1}
	0.08	2	3	3	8^{1}
	0.1	2	3	3	4^{2}
Petragnani	0.01	2	3	3	5^{1}
	0.02	2	3	4	5^{1}
	0.04†	2	3	4	4^{1}
	0.06	2	3	4	5
	0.08	3	3	5	0
	0.1	3	4	5	6^{1}

* The numeral indicates the number of weeks when growth first appeared. An exponent (1 or 2) designates the number of positive tubes; no exponent = all three tubes positive.

† This is the approximate concentration of malachite green used by Petragnani.

The dye in these amounts is not a cidal dye but rather acts only as a static dye in concentrations up to 0.1 per cent in these media. It is interesting also that the tubercle bacilli are able to decolorize malachite green around the colonies in the egg medium, vitiating to some extent the contrast color value; this may lead even to deception of extent of growth if not read carefully.

SUMMARY AND CONCLUSIONS

1. The addition of potato or potato products to egg-yolk does not appear to add any value to the latter as nutrient for human or bovine tubercle bacilli and is unessential for diagnostic culture for tubercle bacilli.

2. The addition of malachite green in concentrations of 0.01 to 0.1 per cent to egg media tends to retard particularly the growth from small plantings of human and bovine tubercle bacilli. In these concentrations, the dye acts as a static agent but not as a cidal agent. In the close proximity of colonies of mammalian tubercle bacilli, the malachite green in egg-yolk or Petragnani's medium is reduced and loses its color, thus leading to possible error in reading cultures.

3. Petragnani's multiple mixture medium does not appear to be as good a nutrient for the growth of small plantings of mammalian tubercle bacilli as the simple egg-yolk medium, apparently because of the slight retarding effect of the malachite green. Economically, it is less easily prepared consistently.

4. If color contrast is desired in a nutrient medium for the diagnostic growth of small numbers of mammalian tubercle bacilli, such coloring material should be of the most striking contrast value. This dye should be nonstatic and stable. It should be incapable of reduction or discolorization by the growing bacilli. It should not color the tubercle bacilli themselves. Such a dye is now in contemplation.

SUMARIO Y CONCLUSIONES

1. La adición de patatas o productos de patatas a la yema de huevo aparentemente nada agrega a la última como principio nutriente para los bacilos tuberculosos humanos o bovinos y no es indispensable para los cultivos de bacilos tuberculosos con mira al diagnóstico.

2. La adición de verde de malaquita a concentraciones de 0.01 a 0.1% a los medios de huevo tiende a retardar en particular las colonias de las pequeñas siembras de bacilos tuberculosos humanos y bovinos. A esas concentraciones el colorante actúa como agente estático pero no bactericida. En la proximidad inmediata de las colonias de los bacilos tuberculosos de mamíferos, el verde de malaquita agregado a la yema de huevo o al medio de Petragnani es reducido y pierde su color, lo cual puede motivar errores al interpretar los cultivos.

3. El medio de mezcla múltiple de Petragnani no parece ser tan buen nutriente para el desarrollo de las pequeñas siembras de bacilos tuberculosos de mamíferos como el simple medio de yema de huevo, aparentemente debido al ligero efecto retardador del verde de malaquita. Desde el punto de vista de la economía, aquél por lo general también es menos fácil de preparar.

4. Si se desea un contraste crómico en un medio nutriente para el cultivo de pequeños números de bacilos tuberculosos de mamíferos, con mira al diagnóstico, el colorante debe mostrar el más notable contraste. Tampoco debe ser estático aunque estable y debe resistir la reducción o decoloración por parte de los bacilos en desarrollo, pero sin tenir los bacilos tuberculosos mismos. Un colorante de esa naturaleza se halla ahora en estudio.

REFERENCES

(1) Corper, H. J., and Uyei, Nao: The isolation of tubercle bacilli from contaminated tuberculous materials, Am. Rev. Tuberc., 1927, *16*, 299; J. Lab. & Clin. Med., 1929, *13*, 469.

(2) Corper, H. J.: The certified diagnosis of tuberculosis, J. A. M. A., 1928, *91*, 371.

(3) Corper, H. J., and Cohn, M. L.: The nutrient quality of eggs for growing tubercle bacilli, Am. J. Hyg., 1933, *18*, 1.

(4) Schwabacher, Herta: A comparison of different media for the growth of the tubercle bacillus, Tubercle, 1937, *18*, 199.

(5) McCarter, Janet R., and Kanne, Elizabeth M.: Egg mediums for the isolation of all three types of tubercle bacilli, J. Infect. Dis., 1942, *71*, 102.

(6) Petroff, S. A.: A new and rapid method for the isolation and cultivation of tubercle bacilli directly from the sputum and feces, J. Exper. Med., 1915, *21*, 38.

(7) Corper, H. J., and Cohn, Maurice L.: Media for tubercle bacilli: An evaluation of different media for diagnostic cultures of tubercle bacilli, Am. Rev. Tuberc., 1942, *46*, 560.

(8) Ordway, W. H., Medlar, E. M., and Sasano, K. T.: Routine application of concentration, culture, and guinea pig inoculation for the demonstration of tubercle bacilli in tuberculous cases under treatment, Yale J. Biol. & Med., 1942, *15*, 353.

(9) Sasano, K. T., and Medlar, E. M.: Egg-yolk-potato medium: Its efficacy for demonstrating small numbers of tubercle bacilli, Am. Rev. Tuberc., 1943, *48*, 297.

(10) Powelson, Dorothy M., and McCarter, Janet R.: Cultivation of human tubercle bacilli on egg mediums, J. Infect. Dis., 1944, *75*, 95.

TUBERCULIN ALLERGY IN PATIENTS CRITICALLY ILL WITH TUBERCULOSIS[1]

C. EUGENE WOODRUFF

It is well known that tuberculous patients in the terminal stages of their illness frequently lose the capacity to react to the usual skin-test doses of tuberculin. In 1908 von Pirquet (1) noted that tuberculin sensitivity is frequently lost in cachectic states, or when the patient becomes moribund. Mantoux (2), also, observed that patients may become anergic to tuberculin in measles, meningitis, miliary tuberculosis and in advanced disease with marked toxemia. However, the time element in the loss of sensitivity, which is the subject of the present study, has not been adequately studied heretofore. Data obtained from tuberculin tests on 54 patients, 16 years of age or older, who died at the Wm. H. Maybury Sanatorium during the five-month period, January 14 to June 14, 1944, constitute the material on which this study is based.

METHODS

On admission to the Sanatorium, all patients are given an intracutaneous tuberculin test using 0.1 ml. of a 1:10,000 dilution of OT[2] (0.01 mg.). The tests are observed at the end of forty-eight hours; an area of induration 5 mm. or more in diameter being considered a positive test. Patients negative to the first dilution are retested at forty-eight-hour intervals with tuberculin ten times as concentrated, the final dilution used being 1:10 OT (10 mg.). Following these admission tests, when a patient's name appeared on the critical list he was similarly tested, at monthly or more frequent intervals, an attempt being made to obtain a sensitivity reading within ten days or less of his death.

From the various sensitivity readings, curves which represent the changes in the allergic state of each patient have been plotted. In constructing these curves the sensitivity levels were indicated as 0, 10, 100, 1,000 and 10,000 depending upon the dilution of tuberculin to which the patient proved sensitive. For example, a minimal positive reaction (that is, a 5 mm. reaction) to 1:10,000 OT was plotted directly on the 10,000 level. Similarly, 5 mm. reactions to 1:1,000, 1:100, and 1:10 OT were plotted respectively on the 1,000, the 100 and the 10 levels. The 0 level, for patients who failed to react to 1:10 OT, was placed arbitrarily a short distance below the 10 level. Interpolations between the various levels were made as follows: a 10 mm. (average diameter) reaction to 1:1,000 OT was plotted one-fourth of the way up toward the 10,000 level. A 15 mm. reaction was plotted one-half the way between the two levels, while a 20 mm. reaction was plotted three-fourths of the way up. The abscissae on the graph represent the time in weeks before the death of the patient.

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

[2] Furnished by Parke, Davis & Company, Detroit, Michigan.

SENSITIVITY CURVES

The data for a representative case will be given in detail along with essential facts from the patient's history.

Case 7: W. M. W., colored female, age 35, admitted to Wm. H. Maybury Sanatorium November 13, 1942 complaining of pain in the left chest. For about a year the patient had had some pain on the left side and for the past six months had had occasional bouts of fever. Loss of weight during the year amounted to 15 lbs. The admission X-ray film showed a minimal tuberculous process in the infraclavicular region on both sides. The sputum was negative for tubercle bacilli on repeated examinations, including one culture. For one year after admission the patient's temperature remained practically normal though repeated X-ray examinations of the chest showed a persistent slight increase in density of the pulmonary lesions bilaterally and, on October 18. 1943, showed a small cavity on the right. Pneumothorax was attempted but was unsuccessful. The patient's sputum became positive for tubercle bacilli. She complained repeatedly of abdominal pain. A gastrointestinal series showed no evidence of tuberculous enteritis, but pelvic and rectal examinations revealed generalized tenderness on all walls of the pelvis. Early in December, 1943 the patient's temperature rose abruptly to a maximum of 105.6°F. A Mantoux test revealed a 5 mm. reaction to 1:10,000 OT. From this time on the patient's course was slowly downhill. A roentgenogram made March 15, 1944 showed an increase in disease in the upper third of the right lung and throughout the entire left lung. There were bilateral cavities, that on the left extending from the apex almost to the base of the lung. The patient died May 1, 1944. Permission for autopsy was not granted. From the course of her disease, as well as signs and symptoms, the clinical diagnosis included tuberculous salpingitis along with extensive pulmonary tuberculosis.

Table 1 gives the data for the various sensitivity readings on the above patient, while in chart 1 will be found curve no. 7 which was constructed from these data. The drop in sensitivity during the last three weeks of the patient's life is pronounced.

As already noted, sensitivity curves have been constructed for all 54 patients included in the present series. Ten of these curves, illustrating the extremes in sensitivity which were encountered, are reproduced in chart 1. For case 1 it will be seen that only a single reference point is given. This means that the patient died too soon after admission for more than one skin test to be performed. Dotted lines have been employed for the curves when the time interval between reference points is several months. Thus in case 9 there is no intervening reference point between the admission test of November 4, 1943, when the patient showed a 12 mm. reaction to 1:10,000 OT, and the skin-test series just before the patient's death, at which time she failed to react to 1:10 OT. While the available data are insufficient for the construction of an accurate curve in this case, one may accept curves 6, 7 and 8 as more or less typical of the terminal changes in sensitivity in those patients who become almost completely anergic before death. The steep downward slant occurred in every case of this sort when sufficient data were available for plotting the curve.

TABLE 1

Sensitivity readings in case 7

DATE	DILUTION OF TUBERCULIN USED	SIZE OF REACTION
12-17-43	1:10,000	5 mm.
1-24-44	1:1,000	15 mm.
3- 5-44	1:1,000	15 mm.
4- 6-44	1:1,000	10 mm.
4-17-44	1:100	5 mm.
4-27-44	1:10	5 mm.

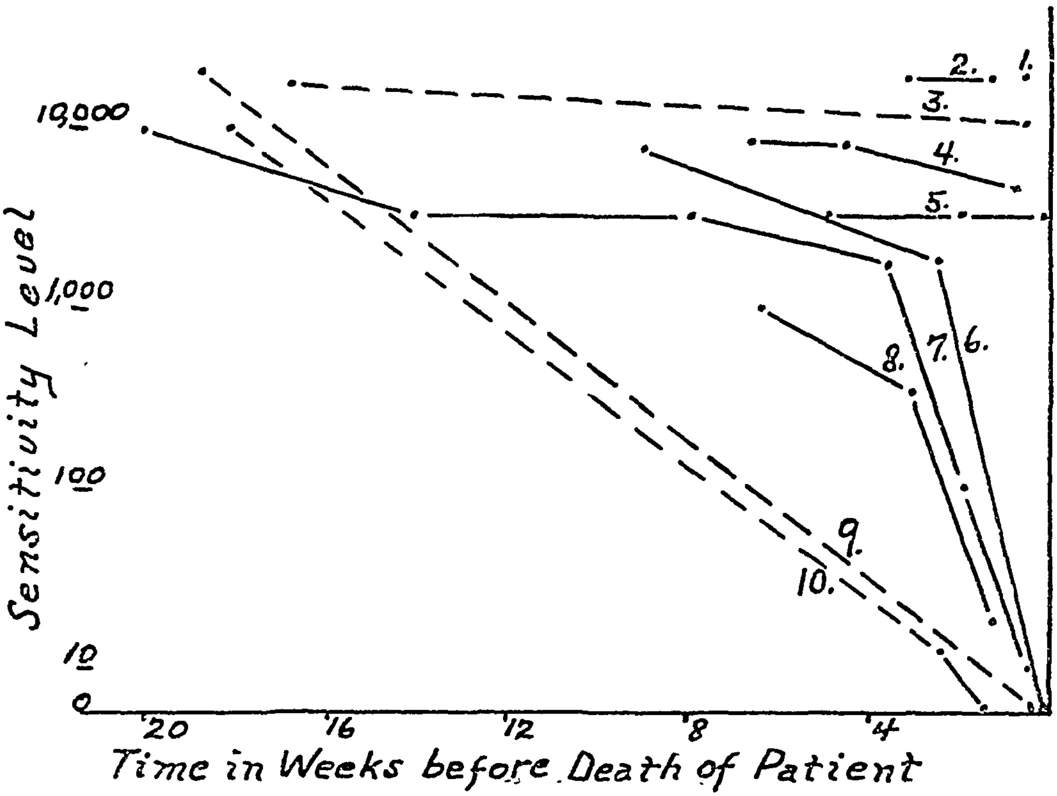


CHART 1. Sensitivity curves

SENSITIVITY LEVEL OF PATIENTS SHORTLY BEFORE DEATH

During the period January 14 to June 14, 1944, 92 Sanatorium patients died. In the 54 cases included in the present series definitive sensitivity readings were obtained within ten days of the death of the patient. The distribution of the 54 patients according to sensitivity shortly before death is shown in table 2. Included in the table is the cause of death of the patient, special attention being given to factors other than pulmonary tuberculosis.

From table 2 it will be noted that more than one-fourth of the patients were in

the lowest sensitivity group, while only 5 of the 54 reacted to 1:10,000 OT shortly before death. The table indicates further that, in the present series, death occurred in the highly allergic patient under only two conditions: if the patient had a fatal hemorrhage, or if he was afflicted with silico-tuberculosis.

The reason for the association between fatal hemorrhage and a high level of sensitivity is evident when one considers that only in hypersensitive tissues does the tubercle bacillus and its products cause tissue destruction (3). In the disease silico-tuberculosis, on the other hand, the factor of silicotic fibrosis is superimposed upon the change induced by the tubercle bacillus alone. Undoubtedly the additional strain which such fibrosis places upon the cardiorespiratory system is an important factor in bringing about the death of these patients while their sensitivity is still at a high level.

The rôle of chronic nephritis as a cause of death in the present series of patients deserves more extensive study. Some of the nephritic patients had little or no active pulmonary tuberculosis. It is hoped that this aspect of the problem can be studied more carefully when a larger group of cases has been accumulated.

TABLE 2

Allergic condition of patients and cause of death

SENSITIVITY GROUPS			CAUSE OF DEATH			
Sensitivity level	Number of cases	Per cent	Pulmonary hemorrhage*	Silico-tuberculosis	Nephritis	Pulmonary tuberculosis
10,000 or above	5	9.2	3	2		
1,000 to 10,000	16	29.6	2	3	6	5
100 to 1,000	16	29.6		1		15
10 to 100	3	5.6				3
Below 10	14	26.0				14
Total............	54	100				

* It should be understood that all of the patients who died following pulmonary hemorrhage also had pulmonary tuberculosis.

The patients in the lowest sensitivity groups will be found listed with pulmonary tuberculosis as the cause of death. However, most of these patients also showed disseminated tuberculosis, with miliary tubercles in liver and spleen.

DISCUSSION

While a considerable proportion of tuberculous patients become almost completely anergic during the final weeks of illness, it is evident from the sensitivity curves that the human organism clings with great tenacity to this fundamental response to infection—allergy. In fact it is only after the patient has begun to refuse food and is obviously in a terminal condition that he will fail to react to the 1:10 dilution of tuberculin. Compared to the volatile temperature curve, with its hourly changes, major changes in sensitivity are slow and glacier-like. This is particularly true when the patient's sensitivity is still high, several

months being required, usually, for his sensitivity to fall from the 10,000 to the 1,000 level. Once the 1,000 level has been reached, however, the complete fall in sensitivity to the 0 level may occur in a matter of three weeks.

From the data given in table 2 it is evident that the anergic tuberculous patient no longer needs to fear death from fatal hemorrhage. However, he is exposed to the equally great hazard of death from the uninhibited proliferation of tubercle bacilli in his tissues. Studies on experimental animals (4, 5) as well as on human material (6) indicate that after the complete loss of sensitivity the animal organism loses any capacity which it may have had for inhibiting the growth of tubercle bacilli in its tissues.

Well over 70 per cent of patients, when first admitted to Maybury Sanatorium, are highly allergic, as indicated by a positive reaction to the 1:10,000 dilution of tuberculin. On the other hand, it is evident from table 2 that less than 10 per cent of the patients are at this level of sensitivity when death occurs. Thus it is apparent that, in the great majority of cases, a marked deterioration in sensitivity occurs during the terminal phases of the patient's illness. One might assume from these facts that a decrease in sensitivity in a tuberculous patient would be of serious prognostic import. Actually some workers in the field of allergy in tuberculosis have failed to find any relationship between tuberculin sensitivity and prognosis (7, 8). However, the foregoing workers dealt with only minor changes in sensitivity, such as differences in size of reaction to the same amount of tuberculin. With regard to major changes, such as the fall from the 1,000 to the 100 level of sensitivity, there is much in the literature to indicate a serious prognostic import (9, 10, 11). Our own experience completely corroborates this latter point of view.

SUMMARY

The allergic condition of the tuberculous patient frequently deteriorates rapidly during the last few weeks of life. Death in those patients in whom loss of sensitivity is most complete is due to wide-spread pulmonary tuberculosis, and frequently includes miliary tuberculosis of other organs. In the few patients who retain a high level of allergy, death is usually due either to fatal hemorrhage or to silico-tuberculosis.

A poor prognosis must be given for any patient with active tuberculosis who experiences a marked fall in sensitivity to tuberculin.

SUMARIO

El estado alérgico del tuberculoso frecuentemente deteriora con rapidez en las últimas semanas de la vida. En esos casos, en los que la pérdida de sensibilidad es más completa, la muerte se debe a tuberculosis pulmonar difusa y frecuentemente comprende granulia en otros órganos. En los pocos enfermos que retienen una alergia elevada, la muerte suele deberse bien a una hemorragia letal o a silicotuberculosis.

En todo enfermo con tuberculosis activa que manifieste una decidida baja de la sensibilidad a la tuberculina, debe hacerse un pronóstico desfavorable.

Acknowledgment is made to Mrs. Mary M. Cooke and Miss Mary A. Leaming for much of the technical work involved in this study.

REFERENCES

(1) VON PIRQUET, C.: Die kutane Tuberkulinreaction, Tuberculosis, 1908, *7*, 204.
(2) MANTOUX, C.: L'intradermo-réaction à la tuberculine et son interprétation clinique, Presse méd., 1910, *18*, 10.
(3) RICH, A. R., AND McCORDOCK, H. A.: An enquiry concerning the rôle of allergy, immunity and other factors of importance in the pathogenesis of human tuberculosis, Bull. Johns Hopkins Hosp., 1929, *44*, 273.
(4) WOODRUFF, C. E., AND WILLIS, H. S.: Allergy and desensitization in experimental tuberculosis: The effect of time and dosage, J. Immunol., 1939, *37*, 549.
(5) WOODRUFF, C. E., AND KELLY, RUBY G.: The correlation between anatomical changes and the allergic state in tuberculous guinea pigs, J. Immunol., 1942, *45*, 79.
(6) BROSIUS, W. L., AND WOODRUFF, C. E.: The effect of sensitivity on the distribution of tubercle bacilli in tuberculosis, Am. Rev. Tuberc., 1944, *50*, 473.
(7) SCHWARTZ, W. S., AND HEISE, F. H.: Variations in tuberculin sensitiveness in tuberculous patients, Am. Rev. Tuberc., 1931, *24*, 479.
(8) APPEL, J. M., DOUGLAS, B. H., JOCZ, T. R., AND WILLIS, H. S.: Relation between tuberculin allergy and clinical course, Am. Rev. Tuberc., 1937, *36*, 303.
(9) LOBBAN, J. W.: The significance of the quantitative tuberculin reaction in the prognosis of tuberculosis, Tubercle, 1930, *12*, 19.
(10) MUSACCHIO, F. A.: A tuberculin survey of one thousand cases of active tuberculosis, Am. Rev. Tuberc., 1940, *42*, 120.
(11) FURCOLOW, M. L., HEWELL, BARBARA, AND NELSON, W. E.: Quantitative studies of the tuberculin reaction. III. Tuberculin sensitivity in relation to active tuberculosis, Am. Rev. Tuberc., 1942, *45*, 504.

SULFONES IN EXPERIMENTAL TUBERCULOSIS[1]

Chemical Constitution and Chemotherapeutic Action

M. I. SMITH, E. L. JACKSON AND WM. T. McCLOSKY

Since the early reports by Rist *et al.* in 1940 (1) of the protective action of 4-4′-diaminodiphenylsulfone in avian tuberculosis in rabbits, systematic investigations have been carried out in this and other laboratories (2, 3, 4, 5) in an effort to develop sulfone derivatives of lower toxicity and greater efficacy than the parent substance. The achievements attained so far have been reviewed in a recent publication (6). The present report concerns further attempts in this direction, and though the results are almost entirely negative it seems worth while reporting them since they are instructive from the standpoint of chemical structure and chemotherapeutic action.

EXPERIMENTAL

Four compounds were studied in this investigation to determine their chemotherapeutic effectiveness in experimental tuberculosis in guinea pigs. The first two were supplied by Parke, Davis and Co. and the last two were synthesized in this laboratory.[2] The animal groups, compounds used and dosages administered were as follows:

(*1*) 4,4′-diamino-2-sulfamyldiphenysulfone. There were 20 guinea pigs in this group. The drug was administered orally, as a 10 per cent suspension in 5 per cent gum acacia, in doses of 0.5 g. per kg. once daily.

(*2*) Phenyl-n-propyl sulfone. Twenty guinea pigs in this group were given daily 0.5 g. per kg. for a few days, then the dose was reduced to 0.25 g. per kg. on account of drug toxicity. The drug was given orally as a 10 per cent or 5 per cent suspension in 5 per cent gum acacia.

(*3*) 4-amino-4′-hydroxylaminodiphenysulfone. Ten guinea pigs were used for this experiment and dosage began at 0.25 g. per kg., continued for a few days, then reduced to 0.125 g. per kg. Dosage used was up to the limits of tolerance. The drug was administered orally as a 2.5 or 5 per cent suspension in 2 to 5 per cent gum acacia.

(*4*) N-(p-aminobenzenesulfonylphenyl)-β-alanine. Ten guinea pigs were used in this test. The drug was administered orally as an aqeous solution of the sodium salt, the dose being 0.5 g. per kg. per day.

In addition there were two other groups as follows:

(*5*) Twenty guinea pigs receiving daily 0.5 g. per kg. promin (sodium p,p′-diaminodiphenylsulfone N,N′-didextrose sulfonate) administered orally as a 10 per cent aqueous solution. This group was to serve as a reference standard.

(*6*) Twenty guinea pigs, untreated controls.

The last two groups were also used concurrently in another experiment to

[1] From the Division of Physiology, National Institute of Health, Bethesda, Maryland.

[2] The synthesis of these compounds will be described elsewhere.

determine the efficacy of streptomycin and promin, individually or in combination, the results of which were published recently (7).

All the guinea pigs were of as uniform weight as possible, range 240 to 270 g. They were all inoculated intraperitoneally with 1 mg. tubercle bacilli human strain (A27-Henry Phipps Institute), and treatment was begun the day after inoculation and continued for a period of ninety days, except the animals in group 4 which received the treatment for only thirty days because of the limited supply of the drug. The animals were weighed once a week. Blood levels were determined at the termination of treatment. At death they were autopsied and the extent of tuberculous involvement noted and recorded according to procedures previously described (3, 4, 6). The same operator made all the autopsies and ratings without knowledge of the group to which the animals belonged. At 105 to 110 days after infection all the survivors were killed with chloroform and necropsies and ratings performed as above.

RESULTS

Toxicity: The compounds used in groups 2 and 3 were the most toxic. However, at the dosage level used it is not believed that many animals were lost because of drug toxicity. The compounds used in groups 1 and 4 were well

TABLE 1

Blood levels, mg. per cent. Average of 3 to 5 animals

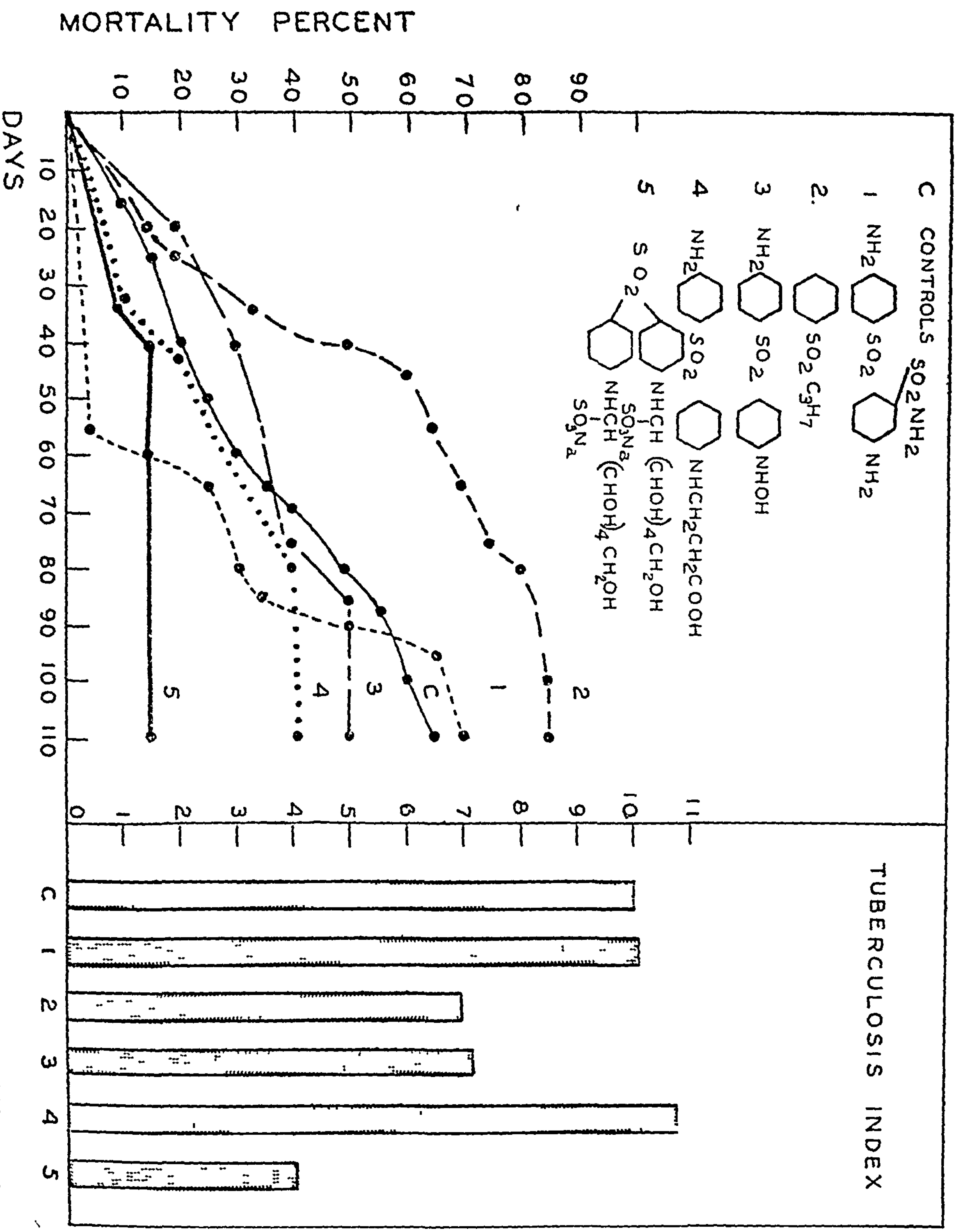
HOURS	COMPOUND 1	COMPOUND 3	COMPOUND 4	PROMIN
3		4.8	1.1	12.0
5	1.1	3.2	0.7	12.8
24	0.7	0.3	1.8	0.5
Dose/day	0.5 g. per kg.	0.125 g. per kg.	0.5 g. per kg.	0.5 g. per kg.

TABLE 2

Summary of the therapeutic efficacy of the several compounds. Experiment terminated at 110 days

	CONTROLS	COMPOUND 1	COMPOUND 2	COMPOUND 3	COMPOUND 4	PROMIN
Mortality per cent at 110 days	65	70	85	50	40	15
Average weight gain in grams	99	59	12	119	131	183
Average spleen weight, grams	5.0	3.5	3.4	3.6	3.9	2.0
Tuberculosis index						
a) Range	5–15	3–18	1–13	2–10	3–18	1–11
b) Average	10.0	10.1	7.0	7.2	10.8	4.1

tolerated, and probably larger doses could have been given, but it is doubtful if the effects would have been any better. Hemoglobin determinations made at sixty days after infection and continuous treatment gave no evidence of deleterious effects, except for the animals in group 3 in which there was a slight to moder-



GRAPH 1. Mortality per cent and "tuberculosis index" in guinea pigs infected with 1 mg. human strain tubercle bacilli intraperitoneally and treated with five sulfones described in text.

ate degree of anemia, the hemoglobin levels being reduced in most of the animals to from 10 to 12 g. per 100 cc.

Blood levels determined at the termination of treatment in groups 1, 3 and 4 showed poor absorption for compounds used in groups 1 and 4, fairly good absorption and retention for compound in group 3. No blood level determinations could be made for compound in group 2 since it has no diazotizable group; however its toxicity clearly indicated good absorption. Table 1 summarizes the results of blood level determinations for the several drugs.

The data on chemotherapeutic efficacy of the several compounds are summarized in table 2 and graph 1. The compounds used in groups 1 and 4 gave no appreciable degree of protection; the animals in groups 2 and 3 showed a lower degree of involvement as compared with the controls, but the slight therapeutic efficacy of these compounds is largely nullified by their excessive toxicity. In any event, their therapeutic efficacy is far less than that of promin.

COMMENT

The lack of activity in compound 2 appears to indicate that activity is associated with amino groups, either free or potentially available as in promin. The inactivity of compound 1 is most interesting, for it differs from 4,4′-diaminodiphenylsulfone only by the sulfamyl group in the benzene nucleus. The parent sulfone though more toxic is certainly at least as effective as promin (2). The lack of activity in compound 4 is consistent with negative results previously obtained with the lower homologue, N-(p-aminobenzenesulfonylphenyl) glycine (6), and may be due to low absorbability. The possibility of chemotherapeutic activity in higher homologues is not excluded. Since the compound, 4-amino-4′-n-propyl-aminodiphenylsulfone, is active even though poorly absorbed (6, 8), it would appear that the substitution of a carboxyl group, as in compound 4, for the terminal methyl group decreases activity.

SUMMARY

Four new sulfones were tested for chemotherapeutic activity in experimental tuberculosis in comparison with promin. None of these compounds showed a degree of activity even approaching that of promin. The results indicate that carboxyalkyl or hydroxy substituents in the amino group reduce activity, that a sulfamyl substituent in the benzene nucleus of diaminodiphenylsulfone reduces absorbability, toxicity and activity, and that at least one free or potentially available amino group in the benzene nucleus of diaminodiphenylsulfone is essential for activity.

SUMARIO

Ensayóse en la tuberculosis experimental la actividad quimioterapéutica de cuatro nuevas sulfonas en comparación con la promina, sin que ninguno de dichos compuestos mostrara actividad siquiera aproximada a la de esta última. Los resultados indican que los sustitutos del carboxialquilo o del hidroxilo, en el grupo amínico, reducen la actividad; que un sustituto sulfamílico en el núcleo

bencénico de la diaminodifenilsulfona reduce la absorbibilidad, toxicidad y actividad, y que para la actividad es esencial que haya por lo menos un grupo amínico libre o potencialmente accesible en el núcleo bencénico de la diaminodifenilsulfona.

REFERENCES

(1) Rist, N., Bloch, F., and Hamon, V.: Ann. Inst. Pasteur, 1940, *64*, 203.
(2) Smith, M. I., Emmart, E. W., and Westfall, B. B.: J. Pharmacol. & Exper. Therap., 1942, *74*, 163.
(3) Smith, M. I., Emmart, E. W., and Stohlman, E. F.: Am. Rev. Tuberc., 1943, *48*, 32.
(4) Smith, M. I., and McClosky, W. T.: Am. Rev. Tuberc., 1945, *52*, 304.
(5) Feldman, W. H., and Hinshaw, H. C.: Am. J. Clin. Path., 1943, *13*, 144.
(6) Smith, M. I.: New York State J. Med., 1945, *45*, 1665.
(7) Smith, M. I., and McClosky, W. T.: Pub. Health Rep., 1945, *60*, 1129.
(8) Feldman, W. H., and Hinshaw, H. C.: Proc. Staff Meet., Mayo Clin., 1945, *20*, 161.

CHEMOTHERAPEUTIC OBSERVATIONS ON TUBERCLE BACILLI[1]

Experiments *in vitro* and *in vivo*

CHARLES J. DUCA AND M. MAXIM STEINBACH

IN VITRO EXPERIMENTS

During the past year and a half, 18 chemical compounds were tested for activity *in vitro* against the tubercle bacillus. These compounds are listed in table 1. Half of them, nos. 1 to 9, were substitution products of diphenylsulfone, that is, (*1*) Na p,p^1-diaminodiphenyl-N,N^1 (dextrose sulfonate); (*2*) Na$_4$,4^1-diaminodiphenylsulfone-2-sulfonacetamide; (*3*) 4-amino-4^1-dodecanoylamino-diphenylsulfone; (*4*) Na-4-amino-4^1-succinylaminodiphenylsulfone; (*5*) disodium disuccinylaminodiphenylsulfone; (*6*) 4,4^1-diaminodiphenylsulfone; (*7*) 4(2,5-dimethyl-N-pyrrolyl)-4^1-succinaminodiphenylsulfone; (*8*) 4,4^1-diaminodiphenylsulfoxide; and (*9*) diphenylsulfone 4,4^1-bisazosalicylic acid. Five, nos. 10 to 14, were sulfonamide compounds, that is, (*10*) N$_1$-benzoylsulfanilamide; (*11*) Na sulfadiazine; (*12*) paraphenylenediamine sulfonamide; (*13*) N^1-dimethylacroyl sulfanilamide; and (*14*) N^1-3,4-dimethylbenzoyl sulfanilamide.[2] The remaining 4, nos. 15 to 18, were various chemical compounds, as follows: (*15*) 4-aminophenyl-2^1-amino-5^1-pyridylsulfone; (*16*) N$_1$glucoside of Na p-aminophenyl-stilbonate; (*17*) sulfanilylcyanamide; and (*18*) 2-S,4-O, pyrimidine.

The above named chemicals were tested together in one experiment, each substance being added, in several concentrations, to Sauton's medium. As a rule, each drug concentration was tested in three flasks. Six flasks without chemical were used as controls. Drug and control flasks were then inoculated with two loopfuls of a thirty-day-old culture of H37 RV (human tubercle bacillus, rough virulent). All flasks were incubated at 37.5°C. for at least three weeks, but some flasks were incubated longer (as indicated in table 1). If no inhibition of growth was observed within three weeks, the particular substance was discontinued. When inhibition of growth was noted in the earlier stages, incubation was continued for a greater length of time. This procedure was followed because temporary bacteriostatic effects, in at least one instance, had previously been observed, that is, promin (1) inhibited the growth of tubercle bacilli for about one month, following which growth started.

The results of the experiments are listed in table 1. Of the diphenylsulfone substitution products, diphenylsulfone 4,4^1-bisazosalicylic acid (no. 9) showed *in vitro* activity comparable to or slightly better than that of promin. Other substances of this series which showed marked *in vitro* activity were promin (no. 1), the sulfoxide derivative (no. 8), and two of the succinyl derivatives

[1] From the Department of Bacteriology, College of Physicians and Surgeons, Columbia University, New York, New York.

[2] Formerly known as Irgafen. Hereafter referred to as no. 14.

(no. 4 and no. 7). Weak bacteriostatic activity was obtained with the antimony compound (no. 16) and the sulfonamide (no. 13). The last two substances

TABLE 1

Effects of various chemical compounds against tubercle bacilli in vitro

	COMPOUND	CONCENTRATIONS TESTED	OBSERVATION PERIOD	CONCENTRATION EFFECTIVE
		mg. per cent		
1	Na p,p^1-diaminodiphenyl-N,N^1 (dextrose sulfonate)	5, 10, 15, 20, 30, 40	6 wks.	Moderate, 20 mg.
2	Na$_4$,4^1-diaminodiphenylsulfone-2-sulfonacetamide	10, 20, 40	1 mo.	None
3	4-amino-4^1-dodecanoyl-amino-diphenylsulfone	10, 20, 40	1 mo.	None
4	Na-4-amino-4^1-succinyl-aminodiphenylsulfone	10, 20, 40	1 mo.	Slight, 40 mg.
5	Disodium disuccinylamino-diphenylsulfone	10, 20, 40	1 mo.	None
6	4,4^1-diaminodiphenylsulfone	5, 10, 15, 20, 30, 40	1 mo.	Slight, 40 mg.
7	4(2,5-dimethyl-N-pyrrolyl)-4^1-succinaminodiphenyl-sulfone	10, 20, 40	1 mo.	Slight, 40 mg.
8	4,4^1-diaminodiphenylsulfoxide	10, 20, 40	1 mo.	Moderate, 20 mg.
9	Diphenylsulfone 4,4^1-bisazo-salicylic acid	10, 20, 40	1 mo.	Complete, 20 mg.
10	N_1-benzoylsulfanilamide	5, 15, 25	3 wks.	None
11	Na sulfadiazine	5, 15, 25	3 wks.	None
12	Paraphenylenediamine sulfonamide	5, 15, 25	3 wks.	None
13	N^1-dimethylacroyl sulfanilamide	10, 20, 40	1 mo.	Slight, 40 mg.
14	N^1-3,4-dimethylbenzoyl sulfanilamide	2, 5, 10, 15, 20, 30, 40	1 mo.	Complete, 20 mg.
15	4-aminophenyl-2^1-amino-5^1-pyridylsulfone	10, 20, 40	1 mo.	None
16	N_1glucoside of Na p-amino-phenyl-stilbonate	10, 20, 40	1 mo.	Slight, 40 mg.
17	Sulfanilylcyanamide	5, 15, 25	3 wks.	None
18	2-S, 4-O, pyrimidine	1, 2, 4, 5, 10, 15, 20, 30, 40	3 mo.	Complete, 20 mg.

Compounds numbered 1, 2, 3, 4, 5, 6, 7, 8 and 15, courtesy of Parke, Davis & Co.

Compounds numbered 9 and 16, courtesy of Burroughs Wellcome and Co.

Compounds numbered 10, 11, 12 and 17, courtesy of Dr. Charles L. Fox, Jr., Department of Bacteriology, College of Physicians and Surgeons, Columbia University.

Compounds numbered 13 and 14, courtesy of Geigy Co.

Compounds numbered 18, courtesy of Dr. Albert Kesten, Department of Biochemistry, College of Physicians and Surgeons, Columbia University.

examined, no. 14, a sulfonamide derivative, and no. 18, thiouracil, both showed activity *in vitro* equal to that of the best of the diphenylsulfones (no. 9).

Of the 18 chemicals tested *in vitro* for effect against the growth of the tubercle bacillus, 8 substances (nos. 2, 3, 5, 10, 11, 12, 15 and 17) were found which had absolutely no inhibitory effect; 5 (nos. 4, 6, 7, 13 and 16) demonstrated a slight inhibiting effect in concentration of 40 mg. per cent; 2 (nos. 1 and 8) displayed a moderate effect at 20 mg. per cent; and 3 (nos. 9, 14 and 18) completely inhibited growth at 20 mg. per cent. It was therefore decided to test *in vivo* 2 compounds which had shown the best bacteriostatic action, and in addition to use diasone (no. 6) which, while it gave poor results *in vitro*, has been reported as effective *in vivo* (2). No. 9 could not be tested *in vivo* because a sufficient quantity was not obtainable at the time of the experiment.

IN VIVO EXPERIMENTS

Forty-eight adult guinea pigs, negative to 1 mg. OT, were infected subcutaneously in the groin with pathogenic bovine tubercle bacilli (Bl), the dose being 0.1 mg. per 500 g. body weight. When tested a week after infection, all guinea pigs reacted to 1 mg. OT intracutaneously. The animals were divided into four groups of 12 each. Group I—thiouracil; group II—diasone; group III—no. 14; group IV—controls. Administration of these chemicals was started two weeks after infection by mixing the respective substances with the food, consisting of guinea pig pellets and oats, supplemented by daily feedings of fresh greens. Diasone and no. 14 were added in 2 per cent concentration, thiouracil in 1 per cent. Four weeks later all substances were used in 1 per cent concentration. Measurement of the daily food intake showed that the guinea pigs ingested about 250 mg. per day of the chemical present at a 1 per cent concentration.

A month after the beginning of treatment, two samples of blood, a week apart, were obtained from guinea pigs which had received diasone or no. 14. The samples were taken in the morning before feedings. Twenty determinations (Marshall method) in each group of animals gave an average concentration of diasone of 5.0 mg./100 cc. blood (3.8 to 6.2 mg.), and of no. 14 of 6.4 mg. (4.8 to 8.5 mg.). No method for determining thiouracil concentrations in blood is known to us. For the first three months all animals were weighed once a week. Guinea pigs which died were autopsied, the surviving animals were killed 210 days after infection when the experiment was terminated. The extent of tuberculous infection was determined by gross inspection, with 4+ indicating maximum involvement of any organ. Sections of lung, liver, spleen and lymph nodes were stained with hemotoxylin-eosin and with Ziehl-Neelsen stain and examined for type of cellular response and number of tubercle bacilli present. Weight changes in the groups are given in table 2, the extent of involvement in table 3. Survival time of the different groups is shown in chart 1.

It will be seen from table 2 that the thiouracil group had gained less weight than any of the others, probably because of some toxic effect of the drug on the guinea pigs. The diasone and no. 14 groups showed gain in weight about midway between the thiouracil and control groups, indicating less toxic effects of these chemicals under the conditions of this experiment.

Table 3 shows that the extent of tuberculosis in all three treated groups was

somewhat less than that seen in the control group. In addition, the type of disease seen in the microscopic sections was approximately the same in the three treated groups. It consisted of hard compact tubercles composed of epithelioid cells and fibrotic tissue and a moderate amount of caseation and necrosis. Acid-fast bacilli, while easy to find, were not numerous. In other words, in the

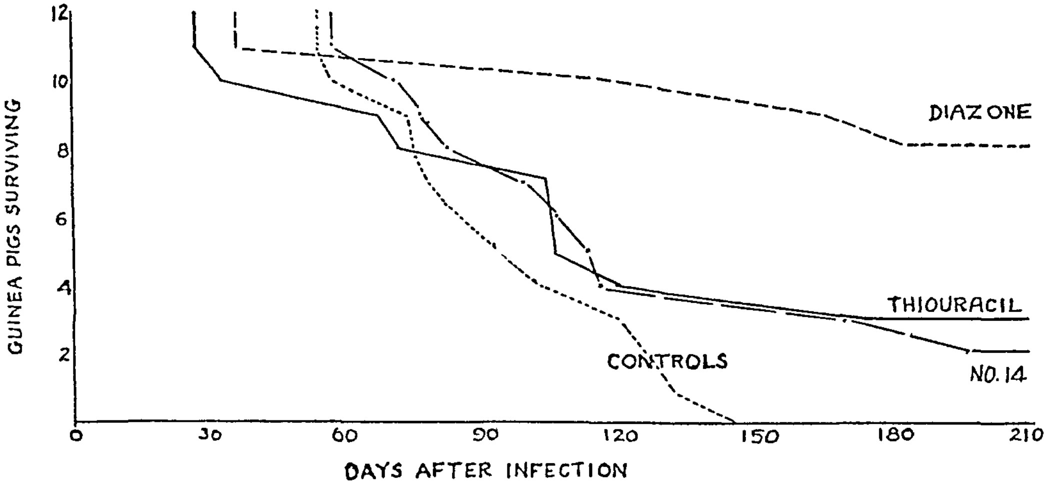


CHART 1

TABLE 2

Weight changes

GROUP	AVERAGE WEIGHT AT INFECTION	AVERAGE WEIGHT 90 DAYS LATER	GAIN IN WEIGHT
	g.	g.	g.
Thiouracil	341	417	76
Diasone	341	477	136
No. 14	332	459	127
Controls	339	516	177

TABLE 3

Extent of tuberculosis

GROUP	LUNGS	LIVER	SPLEEN	LYMPH NODES	SUMMARY
Thiouracil	2.1+	1.7+	2.2+	2.1+	2.1+
Diasone	1.3+	2.1+	2.6+	2.4+	2.4+
No. 14	2.2+	2.8+	2.9+	2.9+	2.8+
Controls	2.6+	3.0+	3.1+	3.1+	3.1+

treated animals the disease appeared to be predominantly fibrotic, with a moderate amount of caseation, and the tubercles were pretty well walled off. However, in the fourth, or control group, the lesions were softer, with less fibrosis, large numbers of mononuclear cells, a great deal of necrosis and caseation, and with little or no attempt at walling off. When the bacilli were counted in three

sections of each organ, organisms were found much more frequently in the controls than in the treated animals.

It is interesting to compare survival time and extent of disease in the different groups. Diasone significantly prolonged the life of the guinea pigs; indeed, not one of the animals in this group can be said to have died of tuberculosis. The 4 animals which died before the end of the experiment showed only 1+, 2+, 2+ and 2+ tuberculosis at autopsy. Eight animals survived until the end, but upon autopsy 6 of these showed quite extensive disease. This was of a fibrotic type, with little proliferation of bacilli. These animals showed a fairly normal rate of growth. It is quite evident that diasone, in the levels found here, inhibits the growth of tubercle bacilli (Bl) *in vivo*; but it does not enable the guinea pig to eliminate the organisms. The other two groups did not differ significantly, in survival time, from the controls. Of these three groups, 4 of the no. 14 guinea pigs, 5 of the thiouracil and 7 of the controls died with enough tuberculosis to be the cause of death. But the controls showed a type of disease different from that in the other three groups. It was more exudative and the bacilli apparently grew well, which was not the case with the treated groups. Evidently thiouracil and no. 14, in the levels attained under the described conditions, inhibited the growth of the tubercle bacillus; but not sufficiently to prolong the life of the animal. It is possible that diasone kept the bacilli at a low enough metabolic level so that toxemia was reduced, although some of the diasone guinea pigs had extensive tuberculosis. The other 2 chemicals, while inhibiting the growth of the tubercle bacillus, did not appreciably prolong the life of the animals.

CONCLUSION

While the compounds no. 14 (N^1-3,4-dimethylbenzoyl sulfanilamide) and no. 18 (2-S, 4-O, pyrimidine) gave complete inhibition of growth at 20 mg. per cent *in vitro*, they retarded only slightly the progress of tuberculous infection in guinea pigs, as compared with corresponding untreated controls. Animals treated with diasone, while showing as much tuberculosis as those treated with thiouracil and no. 14, survived longer and maintained a better nutritive condition.

CONCLUSIONES

Aunque los compuestos No. 14 (N^1-3,4-dimetilbenzoil-sulfanilamida) y el No. 18 (2-S, 4-O, pirimidina) obtuvieron inhibición completa del desarrollo a 20 mg por ciento *in vitro*, sólo retardaron ligeramente la evolución de la infección tuberculosa en los cobayos, comparados con los correspondientes testigos no tratados. Aunque revelaban tanta tuberculosis como los animales tratados con tiouracilo y el no. 14, los tratados con diasona sobrevivieron más tiempo y mantuvieron un estado nutritivo mejor.

REFERENCE

(1) Steinbach, M. M., and Duca, C. J.: Proc. Soc. Exper. Biol. & Med., 1942, *49*, 460.
(2) Feldman, W. H., Hinshaw, H. C., and Moses, H. E.: Am. J. M. Sc., 1944, *207*, 290.

PLEURAL TRANSUDATES[1]

Unusual Roentgenological Configuration Associated with Congestive Failure

AARON E. PARSONNET, EMANUEL KLOSK AND ARTHUR BERNSTEIN

Pleural transudates complicating heart failure are very common. Morgagni, Corvisart and Laennec, all recognized and associated pleural effusion with the failing heart (1). Hydrothoraces occupying either chest present certain well-defined contours making their diagnosis possible through physical and X-ray means (2, 3). Radiographically, these appear as dense shadows whose first delineation is in the costophrenic sinus which is then obliterated. Further accumulations of fluid cause this shadow to spread both medially and laterally along the course of the diaphragm, thus obscuring it and causing the base of the lung to lose its topographical detail. The upper border of this shadow takes on a curved appearance the concavity of which is directed upwards with the lateral extension being higher than the medial one. Lateral exposures show it to extend higher posteriorely than anteriorly. This is the usual configuration seen in the roentgenograms in the conventional position and on physical examination the corresponding Ellis line can be made out, since the fluid rises higher posterolaterally than anteromedially (4). It has been pointed out by several authors, but especially by Rigler, that this fluid level would shift with changes of position and by now it is common knowledge that the assumption of a supine position will spread the fluid over the whole posterior chest in the form of a thin layer (5). Again, Rigler has popularized the lateral decubitus position in which a postero-anterior exposure will show a fluid level in the inferior costal gutter. This shifting fluid level in the thorax is most common with transudates and early inflammatory exudates. However, transudates of long standing or exudates of thick pus, or containing large quantities of fibrin, may show no change with the assumption of various positions (2, 5).

The cause of this configuration of liquid levels in the chest has been ascribed to the following four factors: (*1*) the effect of gravity; (*2*) the elastic recoil and retractility of the lung; (*3*) cohesion and capillarity; (*4*) surface tension of the fluid. The effect of gravity is such that the fluid, the density of which is greater than that of the normal lung tissue, collects in the most dependent portion of the pleural cavity. This force of gravity is opposed by the remaining three forces, the combined resultant of which determines the contour of levels of liquid in the chest. The force of retraction depends upon the elastic recoil of the lung parenchyma which is greatest at the lung periphery, especially at the costophrenic angle. Thus the tendency of the fluid to gather in the costophrenic sinus and rise along the lung periphery is due to the greater retractile power of the lung along this surface. Moreover, the portion of the lung uncollapsed by the collected fluid approximates the chest wall more closely so that the third force, that

[1] From the Cardiac Clinic and Medical Service of Dr. A. E. Parsonnet, Newark Beth Israel Hospital, Newark, New Jersey.

is, that of cohesion and capillarity, comes into play, causing a further rise in the fluid level posterolaterally (6). This force of capillarity not only permits the fluid to rise against gravity, but also allows seepage into the interlobar fissures (7). The anteromedial collections of some fluids, which will be mentioned below, are also due to the action of cohesion.

Retractility and cohesion are both altered by the state of the underlying lung parenchyma and pleural surfaces (6). Chronic passive congestion, pulmonary edema or consolidation alter the elasticity of the lung structure and hence retractility. Pleural adhesions and pleural thickening affect capillarity adversely. Under such circumstances the fluid is more likely to obey the forces of gravity and assume the concave lower border of the inferior surface of the lung and the convex upper border of the superior surface of the diaphragm. The fourth and final factor incriminated in the mechanism and disposition of pleural fluids is the surface tension of the fluid itself. Fluids of low surface tension will follow the laws of gravity more readily than those of higher surface tension.

Not uncommonly, variations of liquid levels may be seen roentgenologically. Four consistent changes in the roentgenological appearance of chest fluid have been described by Rigler, all representing variations in degree of concavity of the Ellis line: *(1)* Straightening of the upper border, simulating a hydropneumothorax, even though no gas is present in the pleural cavity. *(2)* A somewhat convex upper border resembling a high diaphragm. (A case of this type has also been described by Yater and Rodis (8) and Miller (9); we are herein reporting 3 additional cases.) *(3)* Fluid accumulating toward the mediastinal pleura with only a small amount at the periphery; this type may simulate a wide mediastinum or a dilated right auricle. *(4)* Fluid accumulating in the interlobar fissure, simulating encapsulation, although the fluid is entirely free.

During the year 1941, we observed a patient with congestive heart failure who was misdiagnosed for several weeks, because the patient showed signs of sepsis and presented physical signs and X-ray evidence of a high right diaphragm. The X-ray diagnosis was subphrenic abscess. The conventional upright position was used to make the films and no attempt was made to observe shifts in the pleural fluid with posture after the method of Rigler. However, introduction of a small amount of air intraperitoneally quickly demonstrated that the fluid was above the diaphragm and a thoracocentesis revealed a thin serous effusion. After establishing the pneumoperitoneum, the definite Ellis line of the usual roentgenological appearance of a hydrothorax became evident. Perhaps the elevation in the diaphragm was sufficient to bring the lung in closer proximity to the chest wall and allowed the force of capillarity to exert itself. The curved surface of the liquid, characteristic of simple pleural effusion then became apparent. Moreover, the subsequent course of the patient as well as electrocardiographic studies revealed the true nature of the underlying cardiovascular disease.

During the past two months, 2 similar patients were observed; they, too, were cardiacs in chronic congestive failure. The roentgenological diagnosis in each case was an elevated diaphragm due to hepatic congestion. The enlarged cardiac silhouette and the pulmonary congestion in both made the roentgenolo-

gist suspect heart failure, but in each instance the basilar shadow with its convex upper border simulated a high diaphragm and hepatic enlargement was reported. However, the physical findings strongly suggested fluid and aspiration yielded a thin serous fluid with specific gravity, total protein, cytology and bacteriology consistent with a diagnosis of a pleural transudate.

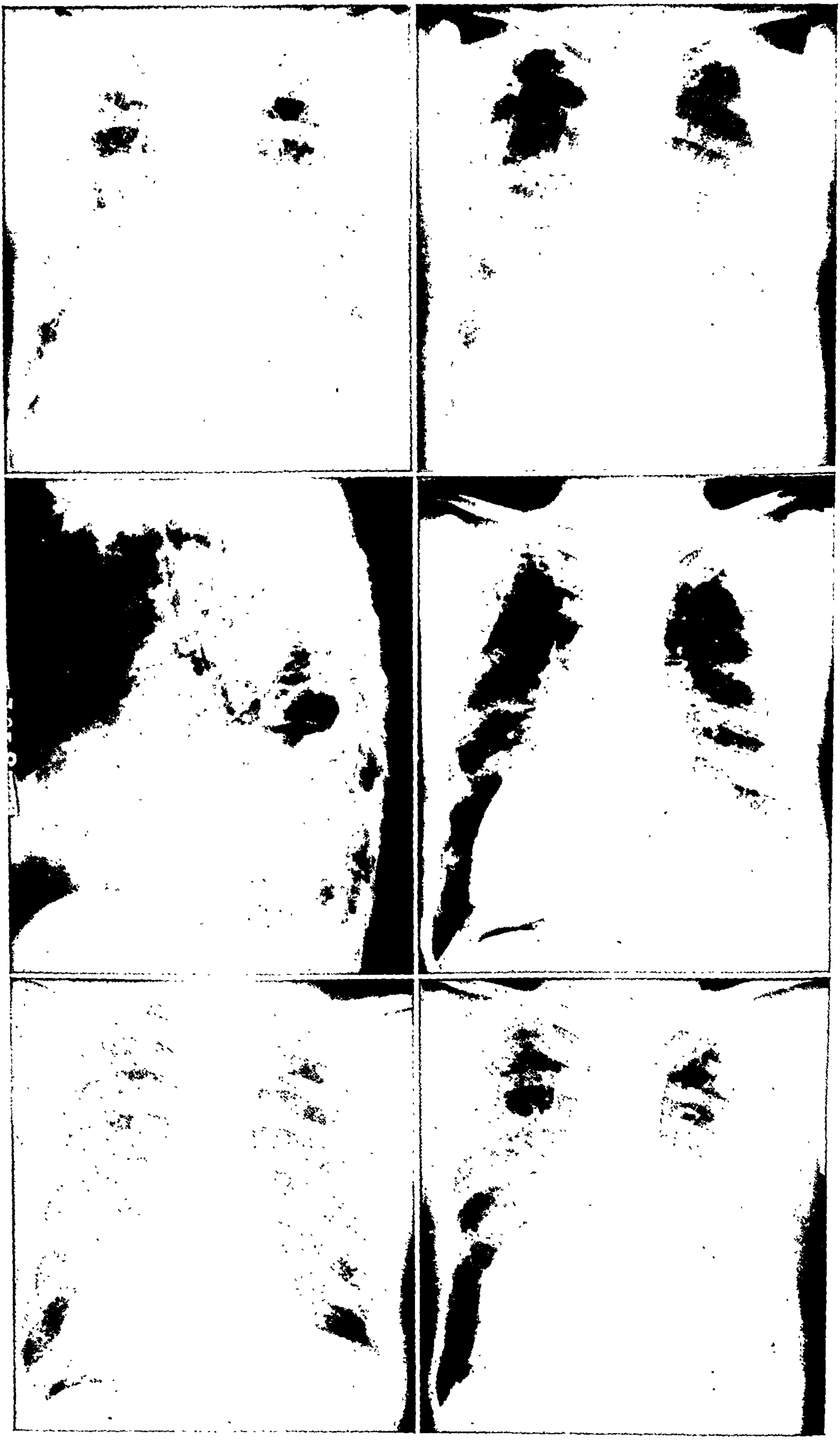
A careful review of the literature yielded only 3 similar cases. Rigler stated that he has seen 6 such cases and reported two (3). Yater and Rodis reported one (8). This was a case of tuberculous serositis with ascites and a left hydrothorax which simulated a high diaphragm. They noted fluoroscopically a fluid wave pass over the effusion with each beat of the heart and the fluid was observed to form a film density in the supine position with the normal diaphragm becoming visible. Miller, in Goldberg's *Clinical Tuberculosis*, states: "On a few occasions one finds typical signs of an effusion in the thorax and on fluoroscopy one is surprized to find a perfectly normal contour to the diaphragm moderately elevated and exhibiting a more or less normal excursion. The physical signs are not at fault, however, and are to be depended upon and, while the findings are similar whether the fluid is above or below the diaphragm, one should not hesitate to do a thoracocentesis. In these conditions the fluid has accumulated between the lung and the diaphragm pushing up the inferior concave surface of the lung and seemingly preserving the normal diaphragmatic contour."

The following 3 cases are reported for the main reason that the significance of the above-described shadows is not generally recognized or properly evaluated despite these early reports. Such atypical fluid accumulations should be carefully considered in the differential diagnosis of subphrenic abscess, hepatic enlargement and eventration of the right diaphragm, especially so if the cardiac silhouette is enlarged, if the lungs show evidences of congestion or if a contralateral effusion exists. Moreover, it may be advisable at times to resort to a diagnostic pneumoperitoneum. In 2 of our cases it was possible to delineate the diaphragm and thus make the fluid clearly visible. That this fluid is free is shown in case 1, by its subsequently assuming the form of an Ellis line and by its seepage into the interlobar fissure. Autopsy examination in case 3 failed to show any evidences of fluid encapsulation.

CASE REPORTS

Case 1: (Figures 1 to 6) J. B., a 60 year old white, retired business man, was admitted to the Newark Beth Israel Hospital on the service of Dr. A. E. Parsonnet, March 10, 1941, with the chief complaints of cough and dyspnea. He had been previously treated at another hospital for pneumonia. His past history was significant in that he had been at the Newark Beth Israel Hospital two weeks before with congestive heart failure due to arteriosclerotic heart disease and a recent myocardial infarction. It was during this admission that the patient became psychotic and had to be transferred to a mental institution where the diagnosis of pneumonia had been made because of a high temperature and physical findings in the right chest.

Physical examination revealed an acutely ill man, dyspneic, orthopneic and slightly cyanotic. Pertinent positive findings were as follows: Dulness posteriorly from the



Figs. 1–6

scapular angle to the base on the right side with distant breath sounds. On the left, the percussion note was also impaired and numerous moist râles were audible. Breath sounds elsewhere were normal vesicular. The heart showed its PMI in the fifth intercostal space outside the MCL. The sounds were of poor tonal quality and there was a short blowing apical systolic murmur; A2 greater than P2; RSR; PR—VR—100. Blood pressure was 118/80. The liver was definitely enlarged and palpable two fingers' breadth below the costal margin. Slight pitting edema of the ankles was present. Temperature was 101.2°F.

X-ray examination on admission was reported as follows: "There is a resolving exudative infiltration of the right base with a pleural effusion of both bases." An electrocardiogram showed a sinus tachycardia with evidences of myocardial damage as seen in coronary sclerosis. The blood count suggested infection with a shift to the left. Blood serology was negative. Blood urea and blood sugar were within normal limits. Sputum showed gram-positive cocci and gram-negative rods.

The patient ran a stormy course with a low grade fever punctuated by sudden sharp rises. On April 4, 1941, an empyema was suspected because of the physical signs and his hyperpyrexia. Roentgenological examination on this day was reported as "excessive elevation of the right diaphragm from probable hepatic enlargement." In order to determine whether the elevated diaphragm was really due to liver enlargement, subphrenic abscess or pleural effusion, 775 cc. of air were instilled into the peritoneum on April 8; this showed that the fluid was above the diaphragm. A thoracocentesis yielded 500 cc. of clear serous fluid, sterile bacteriologically and with a total protein content of 1.75 per cent. Smear showed a few red cells and lymphocytes. On April 11, under fluoroscopic control, 900 cc. of fluid were withdrawn with essentially the same characteristics. Under a regimen of digitalis and mercurial diuretics the patient improved and was discharged from the hospital. The pleural effusion persisted, however, and the patient required frequent treatment with diuretics to control it. Periodic X-ray films showed the right pleural effusion until his demise in 1945. However, the normal X-ray configuration of a simple pleural effusion was seen subsequently with seepage into the horizontal interlobar fissure, as X-ray films in 1943 revealed.

Case 2: (Figures 7 to 10) W. S., a 54 year old white male laborer, was admitted to the Newark Beth Israel Hospital on March 25, 1945, because of mental confusion, semistupor

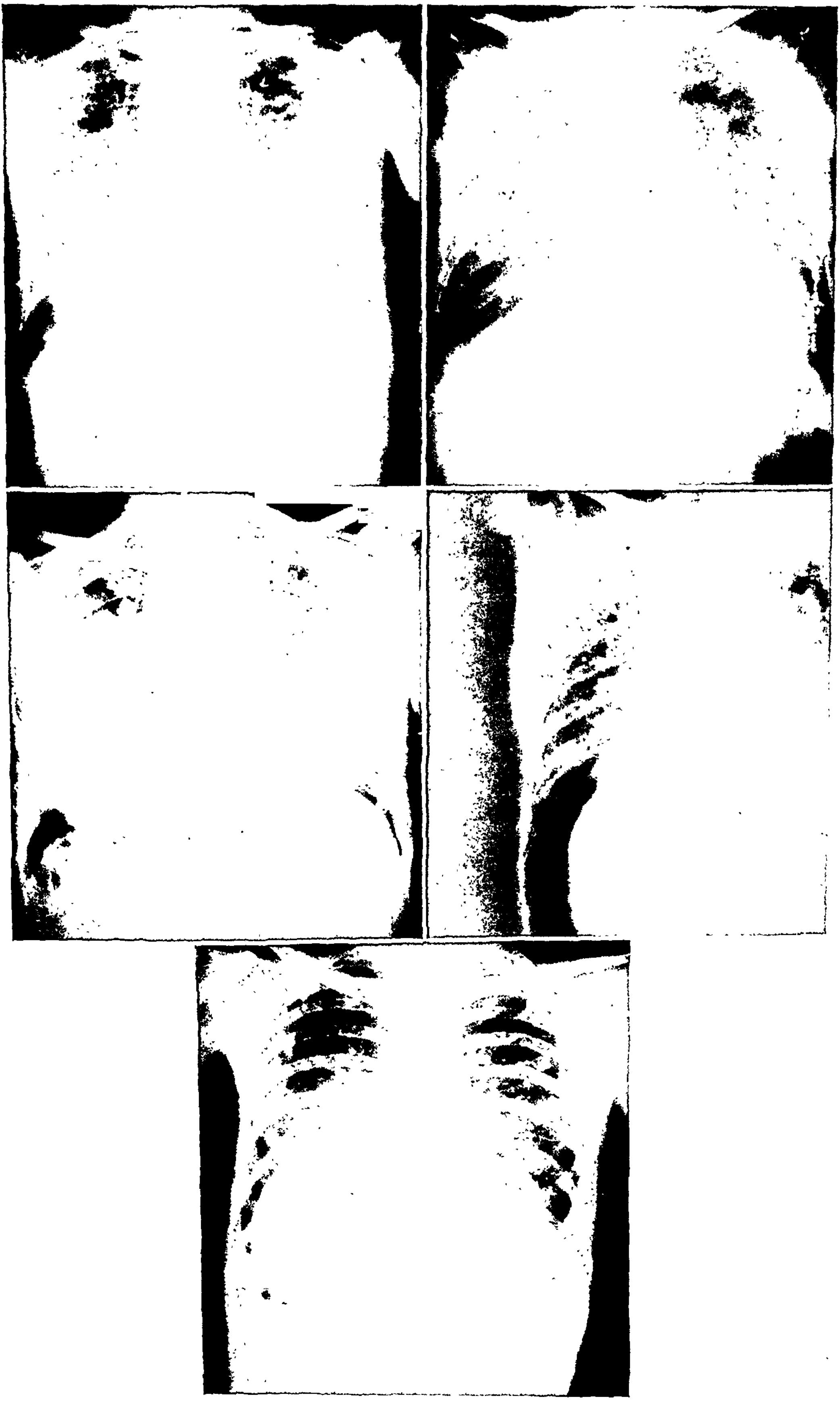
---

FIG. 1. (upper left). Fig. 2. (upper right) and FIG. 3. (centre left). Case 1. Roentgenograms taken on admission showing enlarged cardiac silhouette, especially the left ventricle, the marked increase in the vascular markings in both lung fields and an area of radiopacity in the region of the right diaphragm consistent with a diagnosis of a high right diaphragm due to a subphrenic collection of fluid or hepatic enlargement. Note how the costophrenic angle maintains its acuity. Physical signs, however, suggested fluid and subsequent study showed this shadow to be fluid accumulated between the base of the lung and the diaphragm.

FIG. 4. (centre right). Case 1. A roentgenogram taken after initiation of a pneumoperitoneum. The liver shadow is now separated from the diaphragm and the density is shown to be intrapleural. The convex upper border conforms with the concave inferior surface of the base of the lung.

FIG. 5. (lower left). Case 1. A roentgenogram after the aspiration of 1,400 cc. of fluid from the right pleural cavity.

FIG. 6. (lower right). Case 1. An X-ray film taken three years later, showing the reappearance of the fluid despite mercurial diuretic therapy. That this fluid is free is shown by the fact that the concave Ellis line may be made out and seepage into the horizontal interlobar fissure may be seen.



Figs. 7–11

and shortness of breath. His past history was significant in that he had a resection of the colon for carcinoma in 1938. Physical examination revealed an emaciated adult male, extremely pale. Pertinent physical findings were as follows: Heart—PMI in the sixth space outside the MCL; sounds of fair quality, A2 greater than P2 and accentuated. There was a soft systolic murmur at the mitral area; RSR; PR—VR—92. Blood pressure was 170/130. Eyes and fundi showed marked arterial narrowing, positive Gunn's sign and recent and old exudates with many splinter hemorrhages. Chest: normal pulmonary resonance; normal vesicular breath sounds; medium moist râles were audible on left. The liver was felt four fingers' breadth below the costal margin and there was three-plus pitting edema of the feet and pretibially. He had a moderate secondary anemia with a leucocytosis and shift to the left. Blood urea and sugar were at normal levels. The total serum protein was 5.1 per cent; cephalin flocculation was plus.

The patient's course was steadily down hill, punctuated by episodes of profuse hematemesis and exsanguination, necessitating frequent transfusions. These were proved by X-ray to be due to esophageal varices. The temperature varied between 99 and 104.6°F. Urea nitrogen was reported to vary between 16.6 and 33.0 mg. per cent. The serum protein remained at 5.1 g. per cent. On the 27th, physical examination showed signs of fluid at the right base and an X-ray film of the chest revealed "elevation of the right diaphragm, in all likelihood due to increased intraäbdominal pressure." On July 1, another chest plate showed: "The dome of the right diaphragm is a shade high, in all likelihood due to an increase in pressure in the hepatic area." From the experience with the previous case, fluid was suspected in spite of this report and 900 cc. of a clear serous fluid were aspirated on July 18. An X-ray film several days later still showed the same roentgenological signs and physical examination still revealed the presence of fluid. A pneumoperitoneum was induced, once more separating the diaphragm from the liver shadow and disclosing the pleural fluid which could now be seen to present a typical Ellis line. Again, thoracocentesis yielded 500 cc. of a thin serous fluid. On July 26, after a four-month illness, the patient suddenly expired. No autopsy was obtained.

FIG. 7. (upper left). Case 2. Upright film of the chest showing area of radiopacity in the region of the right diaphragm. The costophrenic sinus is not obliterated. Note marked enlargement of the cardiac silhouette and the hypervascularity of the pulmonic fields. Here again, physical signs suggested fluid and, despite a roentgenological report of a high diaphragm due to hepatic congestion, paracentesis was performed and yielded, 1400 cc. of fluid.

FIG. 8. (upper right). Case 2. Supine film of the chest showing fluid accumulating along the apical and mediastinal portion of the hemithorax. The fluid is therefore free in the pleural cavity, but lies between the diaphragm and the base of the lung in the upright position.

FIG. 9. (centre left). Case 2. Roentgenogram after initiating a pneumoperitoneum. Again the diaphragm is separated from the hepatic shadow and the intrapleural collection of fluid is visualized.

FIG. 10. (centre right). Case 2. Saggital exposure showing fluid accumulated along the mediastinal gutter when the patient is lying with the uninvolved side down and a postero-anterior exposure taken.

FIG. 11. (lower). Case 3. Roentgenogram taken in upright position. Density again is noted in the region of the right diaphragm. The left ventricle is enormously enlarged and the upper contour suggests aneurysmal dilatation of the left ventricle. Hypervascularity of both lung fields is noteworthy. The left costophrenic angle is obliterated. The density noted at the right base was due to fluid as shown by autopsy the following day.

Case 3: (Figure 11) A. D., a 44 year old white male accountant, was admitted to Doctor Parsonnet's service complaining of weakness, dyspnea, orthopnea and ankle edema of one month's duration. Positive physical signs were as follows: White-centered petechiae in each palpebral conjunctiva; dulness and diminished to absent breath sounds in the right lower lobe posteriorly; heart sounds were of poor tonal quality. The PMI in the fifth space outside the MCL; A2 greater than P2; a short apical systolic murmur was audible; RSR; PR—VR—120; liver felt four fingers' breadth below costal margin; temperature 101° F. The blood count showed a moderate leucocytosis with a shift to the left. X-ray films of the chest were again interpreted by the roentgenologist as showing hepatic enlargement and pulmonary congestion. An electrocardiogram showed a sinus tachycardia with left axis deviation and myocardial damage as seen in coronary insufficiency and cardiac enlargement. On careful analysis of the roentgenograms, a clinical diagnosis of left ventricular aneurysm was made. The urine showed 30 red cells per high-power-field; blood culture was sterile; blood urea nitrogen was 33.0 mg. per cent.

Here, again, fluid was suspected based on physical signs, although X-ray films in the upright position failed to record the conventional configuration. The patient's course was progressively downward, with death in three days after admission. The autopsy findings were recorded by Dr. L. Goldman, our pathologist, as follows:

Respiratory tract: The trachea and bronchi are filled with frothy fluid. Both lungs show generalized edema and congestion with some emphysematous bullae in both apices. The right pleural cavity contains about 500 cc. of clear fluid. The left pleural cavity is obliterated by adhesions. The right pleural cavity is entirely patent and no reason for the atypical distribution of fluid discerned.

Circulatory system: Pericardial sac contains about 100 cc. of slightly turbid, yellowish fluid; heart weight—520 g. The epicardium shows numerous areas of fibrosis. The right auricle and ventricle are markedly dilated. There is an aneurysmal dilatation of the anterior wall of the left ventricle with profound myomalacia of the adjoining areas of the intraventricular septum and apical portion of the ventricle. Numerous organized mural thrombi are attached to the endocardium in this area. Both coronary vessels show advanced sclerosis with organized thrombi and evidences of recanalization. The aorta shows moderate sclerosis throughout.

Gastrointestinal tract: With the exception of two hemorrhagic ulcerations in the duodenum, the stomach and intestines are essentially negative. The liver weighs 1,100 g. On section, its cut surface shows evidence of chronic, passive congestion with areas of degeneration and fibrosis. The spleen shows moderate fibrosis.

Genito-urinary tract: The kidneys weigh 340 g. together. There is moderate, passive congestion with little evidence of vascular disease.

Anatomical diagnosis: Sclerosis of both right and left coronary arteries with ventricular aneurysm and mural thrombus formation, associated with myomalacia.

SUMMARY

Three cases of atypical roentgenological appearance of pleural fluid associated with heart failure are recorded, confirming the early, but often overlooked observations of Rigler, and Yater and Rodis. The importance of this observation lies in the fact that a mistaken diagnosis of subphrenic abscess may naturally lead to unwarranted surgery in patients who are decidedly poor surgical risks. Moreover, realization of the fact that such shadow is due to fluid and not hepatic

enlargement may spare the patient much needless suffering by the simple procedure of thoracocentesis.

We wish to add to Rigler's criteria for the roentgenological diagnosis of atypical pleural effusions the aid given by pneumoperitoneum. The procedure should be used especially in cases where mechanical factors may interfere with its redistribution by posture and where the amount of fluid is so small that it cannot be accurately diagnosed by the simpler positioning techniques. We feel that pneumoperitoneum is not an ordeal for even the profoundly sick patient and in some instances may be more readily applied than posturing.

SUMARIO

En los tres casos descritos, un derrame pleural asociado con insuficiencia cardiaca mostró aspecto roentgenológico atípico, confirmando así las antiguas y a menudo inadvertidas observaciones de Rigler y Yater y Rodis. La importancia de esta observación estriba en el hecho de que un diagnóstico erróneo de absceso subfrénico puede conducir naturalmente a una injustificada intervención quirúrgica en enfermos que son claramente malos riesgos quirúrgicos. Además, la comprensión del hecho de que la sombra observada procede del líquido y no de una hepatomegalia puede ahorrar al enfermo mucho sufrimiento innecesario con sólo aplicarle el sencillo procedimiento de la toracentesis.

A las pautas de Rigler para el diagnóstico roentgenológico de los derrames pleurales atípicos, debe agregarse la ayuda aportada por el neumoperitoneo. Este debe usarse sobre todo en los casos en los que factores mecánicos pueden impedir que la postura adoptada redistribuya el líquido y en los que la cantidad de líquido es tan pequeña que no puede ser diagnosticada exactamente por medio de las técnicas más sencillas de cambios posturales. El neumoperitoneo no constituye una prueba dura ni aun para los intensamente enfermos y en algunos casos puede resultar más fácil aplicarlo que hacer cambiar de posición al enfermo.

We gratefully acknowledge the kind coöperation of Dr. Lester Goldman, Pathologist, and Dr. N. James Furst, Radiologist, of the Newark Beth Israel Hospital, Newark, New Jersey.

REFERENCES

(1) Bedford, D. E., and Lovibond, J. L.: Brit. Heart J., 1941, *3*, 93.
(2) Rigler, L. G.: J. A. M. A., 1931, *96*, 104.
(3) Rigler, L. G.: Radiology, 1936, *26*, 543.
(4) Ellis, C.: Boston M. & S. J., 1874, *90*, 13.
(5) Rigler, L. G.: Am. J. Roentgenol., 1931, *25*, 220.
(6) Kaunitz, J.: J. Thoracic Surg., 1935, *4*, 300.
(7) Rigler, L. G.: J. Thoracic Surg., 1936, *5*, 295.
(8) Yater, W., and Rodis, I.: Am. J. Roentgenol., 1933, *29*, 813.
(9) Miller, O. O.: In Goldberg's Clinical Tuberculosis, F. A. Davis Co., Philadelphia, 1944, p. G-38.

EDITORIAL

Pregnancy and Tuberculosis

The relation between pregnancy and tuberculosis has a long record in medical literature. In spite of the time and thought devoted to this subject, it is difficult to follow the golden thread of truth through the zigzag course of medical opinion. Advancing knowledge has multiplied the conditioning factors, and higher standards of living have altered their implications and rendered their application more difficult. Among primitive people with simple environment, physical fitness for motherhood was the major issue; nature ran its course without the full force of the psychic impact of socio-economic factors and religious scruples. If the woman was constitutionally fitted for motherhood, conception initiated a subconscious sense of normal function well performed; the course of pregnancy represented the evolution of manifest destiny and the babe at the breast, the consummation of life's ultimate purpose. The old philosophy—survival of the fittest—caused little anxiety and its unopposed operation set a premium on fecundity and favored emotional equanimity.

Under modern conditions, sexual satisfaction, pregnancy and maternity are hedged about by disturbing inhibitions, inspired by the multifaceted, rapidly mounting socio-economic factors and, in many cases, religious restrictions. A mind so disturbed charges the nervous system with unnatural impulses and they in turn elicit abnormal responses, so the vicious circle leading to psychophysiological imbalance is initiated in virtually every case of pregnancy, varying in degree and significance according to constitutional fitness of the woman and the impact of her socio-economic status.

Add to this the anxiety arising in the mind of the enlightened prospective mother who knows she is tuberculous, understands the danger of contact with the new-born child and the necessity of separation to safeguard the baby against infection, and immediately there arises the need of a skilled obstetrician and a consultant who has had training and experience in the diagnosis and treatment of tuberculosis, both committed to close coöperation in the care of the patient through the course of a normal physiological process influenced by significant psychological conflicts. This need implies highly developed scientific skills and the wise application of the art of medicine.

In the last analysis, it may be said that the woman who is constitutionally fitted for motherhood and not harassed by socio-economic and religious factors may thrive on the profound physiological changes consequent upon pregnancy, even in the presence of tuberculosis. But the woman who is not constitutionally fit, or even the woman possessing constitutional fitness may suffer lowered physical resistance under adverse conditioning factors. With these considerations in mind, it becomes increasingly clear that pregnancy in the presence of tuberculosis, complicated by the difficulties of modern life, may present serious problems, entailing heavy responsibilities.

On the other hand, a summation of our present knowledge and a careful sifting of all the factors, including consideration of improved obstetrical practices and advances in the treatment and the prevention of tuberculosis, surgery playing an important rôle in both, the golden thread of truth emerges from the remaining controversial issues with a more hopeful luster. Accumulated knowledge and experience, weighed by informed observers, justifies the belief that exacerbation or reactivation of tuberculosis in the course of pregnancy seldom occurs in those who are constitutionally fit for this physiological experience, provided the environmental or socio-economic conditions are favorable. In other words, pregnancy *per se* rarely exerts an unfavorable influence upon the course of tuberculosis. In fact, experience causes the careful observer to wonder if it may not occasionally manifest a beneficial influence.

Far too much emphasis has been placed upon pregnancy and tuberculosis. Why not parturition and tuberculosis, the puerperium and tuberculosis, or the endless days and nights of conscientious motherhood and tuberculosis? Nothing can be more devastating, more depleting, than motherly concern centered upon colicky nights and the entailed loss of sleep and physical effort. The tubercle bacillus, though helpless through pregnancy, may revel in the aftermath, especially when emotional moneyless mothers must cut short the puerperium to become nurses, cooks and washerwomen. A good husband, a generous allowance, a push-button puerperium, nurses and maids and other household aids favor equanimity and foster resistance. Through the interplay of all the above factors, the impact of pregnancy upon the mind of the prospective mother may occasionally warrant interruption before the end of the third month. The strain and trauma of abortion after three months approximate that of labor at full term and, with few exceptions, the sacrifice of the unborn child is unwarranted. Even in advanced pulmonary tuberculosis, pregnancy under modern care and labor at or near full term with improved methods and techniques, including cesarean section when indicated, may proceed without unfavorably altering the course of the disease or harming the baby. Tuberculosis is rarely transmitted through the placenta and immediate separation of mother and child eliminates the danger of contact.

After agreeing that a woman with active pulmonary tuberculosis should not become pregnant, nearly all students of this problem believe that pregnancy in women who have had active tuberculosis should not be condoned until after the disease has been apparently arrested and the prospective mother has had two years of normal life. A careful study of the more recent literature indicates that, if pregnancy occurs in the course of pulmonary tuberculosis, the weight of opinion is against interruption, except in rare instances when clear-cut indications arise before the end of the third month. Barring this exception, a viable child free from infection may be anticipated without materially adding to the hazards of the disease in the mother. The immediate separation of mother and child assures the latter a good chance for healthy development if care and environment are favorable. The mother's care during pregnancy and following parturition

should be the same as that accorded similar patients in whom pregnancy is not an associated factor. This includes institutional care and surgical collapse. Not only may it be said that collapse therapy is not contraindicated by pregnancy, but, on the contrary, pregnancy may proceed with much greater security because of it. Perhaps the safest time for a tuberculous woman to have children is during the period of satisfactory collapse therapy.

LEWIS J. MOORMAN

Philip Hale Pierson

1886–1946

Philip Hale Pierson was born November 7, 1886, in Poutingfu, China, where his father, Isaac Pierson, was a Presbyterian missionary. Philip inherited and maintained throughout his life his father's strict faith. He was graduated from

Philip Hale Pierson

1886–1946

Medford High School in Medford, Massachusetts, and in 1908 from Yale University, where one of his ancestors, Abraham Pierson, had been first President of the University. In 1913 he was graduated from Harvard Medical School, later interning at Boston City Hospital and the Massachusetts General Hospital. In 1915 he came to San Francisco to be associated with Dr. Philip King Brown. The following year he became a member of the teaching staff of Stanford University Medical School and since 1933 had held the rank of Clinical Professor of Medicine. In 1935 he was appointed Consultant and Chief of Staff of the Stan-

ford Tuberculosis Service at the San Francisco Hospital. He had been a Consultant in Diseases of the Chest at the Veterans' Hospital, Fort Miley, San Francisco, since that hospital was built.

Doctor Pierson was a Fellow of the American Medical Association and the American College of Physicians, and former President of the California Tuberculosis Association. At the time of his death he was Vice-President of the National Tuberculosis Association. He was a member of the Commonwealth Club and the Alta Vista Lodge of Masons, and a Trustee and member of the Board of Directors of the Calvary Presbyterian Church.

Doctor Pierson's contributions to the science and practice of medicine are many and varied and for the most part have dealt with various phases of tuberculosis. However, his study of *Pulmonary Alveolar Adenomatosis in Man* is a noteworthy contribution to this subject. His study of *Solitary Foci of Tuberculosis* (American Review of Tuberculosis, 1942, *45*, 75) is an outstanding contribution of its kind.

The end came suddenly from cerebral thrombosis on January 17, 1946, at the age of 59. Doctor Pierson is survived by his widow, Grace F. Pierson, and by three children, Dr. Robert E. Pierson, Mrs. Randolph M. Forbes and Mrs. William L. Bush, as well as three grandchildren. To all who enjoyed the privilege of being closely associated with him, Doctor Pierson was a firm friend and a good companion. To his patients he was always the able and sympathetic physician.

Sidney J. Shipman

Alfred Goetzl

1873–1946

Doctor Alfred Goetzl, the former head of the Tuberculosis Division of the City of Vienna (Austria), died in San Francisco, January 21, 1946. Born in Vienna in 1873, he was for years resident physician in the "Sanatorium Alland," at that time the only sanatorium for tuberculous patients in Austria. The Austrian Government appointed him, in 1916, organizer of the campaign against tuberculosis. In 1919 he was commissioned to draw up the regulations concerning tuberculosis in Vienna. From 1921 to 1938 he was head of the Division for Tuberculosis in the Health Department of that city. Alfred Goetzl was also honorary secretary of the Austrian Tuberculosis Association and Editor of its Journal. In all these positions he carried out a great work in organizing and helping the organization of tuberculosis sanatoria and dispensaries and welfare work for the tuberculous. He built up the welfare work for treatment and control of tuberculosis in Vienna. As Associate Professor, he lectured on tuberculosis in the Medical School of the University of Vienna and in nurses training schools. He published more than a hundred articles about tuberculosis, its clinical aspects as well as its social aspects and causes.

The last years of his life Doctor Goetzl lived in San Francisco. There he wrote, in collaboration with R. A. Reynolds, a biography of Doctor J. Tandler, the famous anatomist and reformer of Public Health work in Vienna.

Ludwig Teleky

NOTICE

In an Editorial from the Office of the Chief, Tuberculosis Control Division, published in Public Health Reports, March 1, 1946, it is announced that "Through the courtesy of the Division of Public Health Methods, it is now possible to publish, in the first week of every month, a special tuberculosis issue of PUBLIC HEALTH REPORTS." This is only one manifestation of the expanding activities of the Tuberculosis Control Division, and others are briefly enumerated in this Editorial. The REVIEW extends a cordial welcome to this newcomer in the field of periodical literature on tuberculosis. As far as possible, the papers published in these special issues of Public Health Reports will be abstracted for publication in the Abstract Section of the REVIEW.

NOTICE

Philip H. Pierson Memorial Medical Research Fund

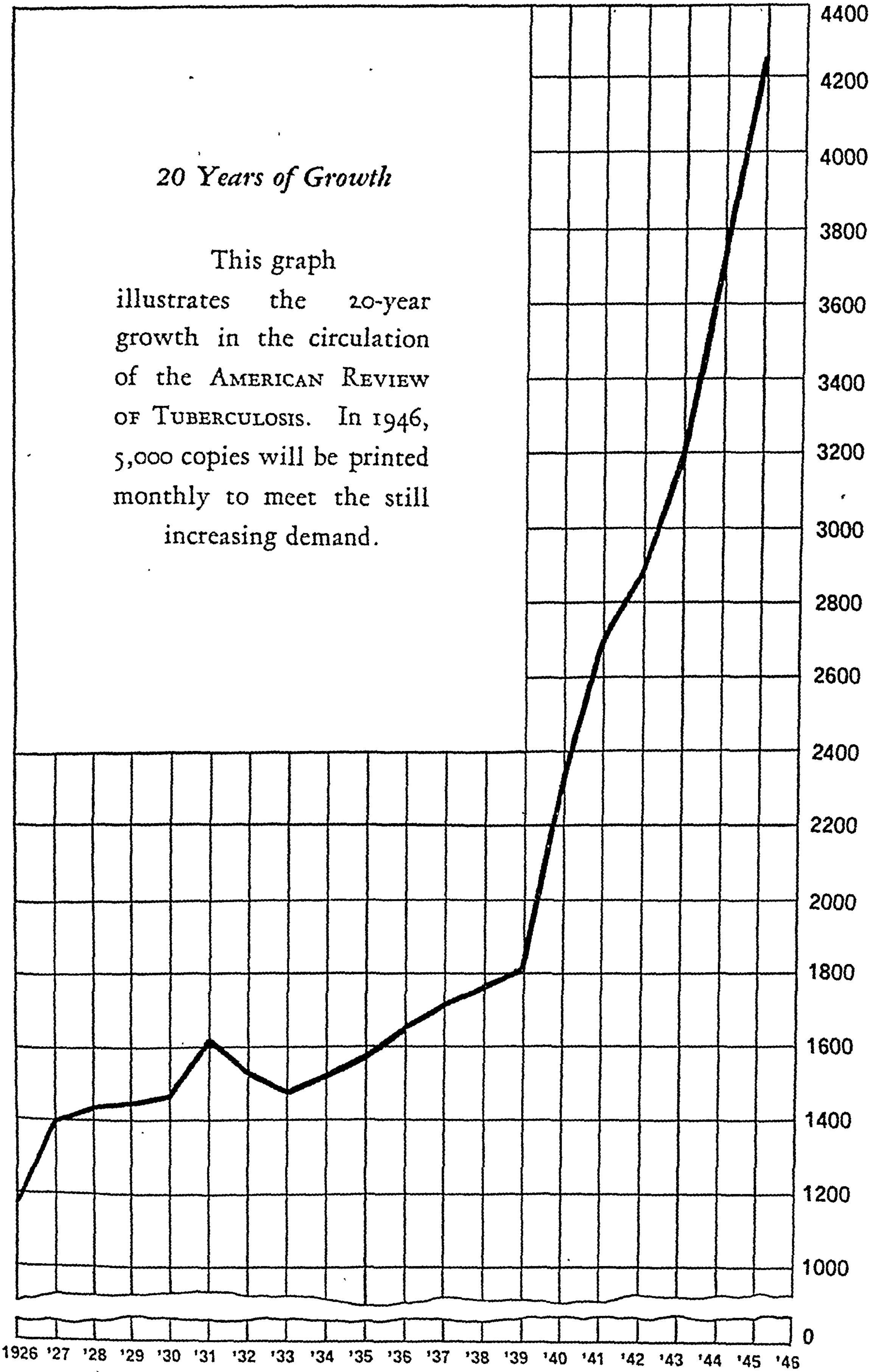
It has been announced by Dr. Harold Guyon Trimble, Chairman of the Board of Trustees of Alum Rock Sanatorium, that a gift of $5,000 has been received for medical research.

Alum Rock Sanatorium, San Jose, California, is a non-profit institution for the treatment of diseases of the chest.

This gift will establish the Philip H. Pierson Memorial Medical Research Fund as a dedication to his unselfish devotion and scientific attainments in the field of medicine, particularly diseases of the chest. Doctor Pierson, Clinical Professor of Medicine at Stanford University Medical School and consultant at Alum Rock Sanatorium, died unexpectedly on January 17, 1946.

20 Years of Growth

This graph illustrates the 20-year growth in the circulation of the AMERICAN REVIEW OF TUBERCULOSIS. In 1946, 5,000 copies will be printed monthly to meet the still increasing demand.



INDEX OF SUBJECTS AND AUTHORS

THE AMERICAN REVIEW OF TUBERCULOSIS

OFFICIAL JOURNAL OF THE AMERICAN TRUDEAU SOCIETY

ABSTRACTS

VOLUME LIII

JANUARY-JUNE, 1946

PUBLISHED MONTHLY

AT MOUNT ROYAL AND GUILFORD AVENUES, BALTIMORE 2, MD.

BY THE NATIONAL TUBERCULOSIS ASSOCIATION

THE

AMERICAN REVIEW OF TUBERCULOSIS

ABSTRACTS

VOLUME LIII JANUARY, 1946 ABST. No. 1

Air-borne Tuberculosis.—If normal guinea pigs are placed in individual cages in an ordinary animal room housing tuberculous animals, the exposed pigs acquire tuberculosis of respiratory origin. Those at a distance acquire tuberculosis just as often as those in the immediate proximity. Several experiments were conducted with inbred rabbits of varying resistance to tuberculosis. In the first, they were put in individual cages separated by a wire mesh screen from a runway for infected rabbits which shed tubercle bacilli in their urine. The disease acquired is of respiratory origin beginning as a single primary focus. The disease acquired by these families closely corresponds to the different types of tuberculosis seen in man. The second experiment was carried out by using the same type of housing, but having one room and its quarters irradiated and the other not irradiated by ultraviolet rays. Litter mates of both high and low resistance were placed in corresponding positions in the contact cages of both rooms, and the rabbits serving as the source of infection were interchanged daily between the two rooms. At the end of one year, 11 of 15 contacts in the nonirradiated room died of tuberculosis. None of the 15 litter mates in the irradiated room acquired tuberculosis. Three animals in the control room developed tuberculin sensitivity, but no tuberculous changes were found at autopsy. It is therefore probable that ultraviolet radiation may control air-borne contagion of human tuberculosis. It was noted that resistance to attack by air-borne contagion is distinct from resistance to progression of the ensuing disease. In similar experiments, but with an increase in the number of bacilli in the environments, there was shown in rabbits of high resistance to disease an increased incidence of infection, acceleration in rapidity of the attack and an affect on the essential character of the disease in proportion to the concentration of the infectious agent. In rabbits of low genetic resistance to tuberculosis, increasing the concentration of tubercle bacilli also increases the incidence of the disease and accelerates its onset. The character of the disease is not affected, it remaining a rapidly progressive and disseminating type. Beyond a certain concentration, further increases in the infecting agent produced no effect.—*Experimental Air-Borne Tuberculosis, M. B. Lurie, Am. J. M. Sc., February, 1945, 209: 156.—(G. F. Mitchell)*

Pulmonary Lesions Due to Waxy Fraction of Tubercle Bacillus.—The endotracheal injection of the waxy fraction of tubercle bacilli in guinea pigs caused the formation of granulation tissue, fibrosis and occasional giant cells.—*Ricerche istologiche sulle lesioni polmonari prodotte dalle cere del B. K. iniettate per via endotracheale, S. Savarino, Ann. Ist. Carlo Forlanini, 1942, 6: 730.—(G. Simmons)*

Specific Proteolytic Enzymes in Pleural Effusions.—In 73 out of 75 cases of pleurisy with effusion and in 20 out of 26 cases of subsiding pleurisy with effusion, the urine contained specific proteolytic defense enzymes. Three different products of the tubercle bacillus were used for the demonstration of such ferments: (*1*) caseous substance, giving 66 per cent; (*2*) endoproteins, giving 70 per cent; and (*3*) esoproteins obtained from cultures,

giving 61 per cent of positive results. These findings confirm the opinion of most workers in this field that pleurisies with effusion are always of tuberculous origin.—*Sulla natura tubercolare delle pleuriti clinicamente primitive: La ricerca delle proteasi specifiche di difesa nei pleuritici, C. Cattaneo & B. Mariani, Ann. Ist. Carlo Forlanini, 1942, 6: 145.—(G. Simmons)*

Allergy after BCG Vaccination.—After BCG vaccination the sensitivity against tuberculin is increased. There is a marked tendency to relate this postvaccinal allergy to certain general characteristics of the morphological and local types in order to explain the individual variations. The general constitution as well as certain skin diseases play a definite rôle in increasing the sensitivity against tuberculin. The authors have found a marked contrast in postvaccination allergy in the young adult and in the newborn. It is more rapid and intense in the young adult and is retarded in the newborn. Four hundred and eighty-nine young male adults (23.6 per cent of the total examined) between 18 and 23 years who were anergic to tuberculin in concentrations from 1:10,000 to 1:10 (Mantoux technique) have been studied. They were vaccinated by intracutaneous injection of 0.15 mg. of BCG in physiological salt solution. Within four to twenty-eight days these persons were subjected in groups to the Mantoux test. From the fourth to the fifteenth day a dilution of 1:10 of Old Tuberculin, and from the twentieth to the twenty-eighth day of 1:100 was employed. The group tested on the fourth day showed entirely negative skin tests. The group tested on the ninth day showed 9.7 per cent positive results. The positive results were more frequent in groups tested after the ninth day and finally reached 85.7 per cent on the twenty-eighth day. It is assumed that these young adults had not been infected with tuberculosis prior to their vaccination. The proof is found in the fact that on the fourth day after the application of BCG none of the tested persons showed any reaction to tuberculin and that the allergization started only after the ninth day. Secondary proof is that no case of positive Koch phenomenon with early suppuration was observed, although this is quite frequent in cases of vaccination of persons with primary infections. The authors also studied the local conditions of the skin and the possibility that these could influence the establishment and intensity of allergy. According to the color of the skin, four groups (white, swarthy, brown and black) and according to the hairiness, three groups (hairless, hairy and hirsute) were tested separately. The results showed that in these seven groups there was no difference in the intensity or chronology of the allergy produced after vaccination with BCG. A series of 218 newborn received before the seventh day of life 0.15 mg. of BCG by intracutaneous injection. The appearance of a positive Mantoux test was also investigated. The babies were divided in groups. These were tested by intracutaneous injections of 1:10 tuberculin from the fifteenth day to the fourth month after vaccination. None of the children showed an allergic reaction on the fifteenth day. After one month only 12.3 per cent showed a positive skin test; after two months, 60 per cent; after three months, 65 per cent; and after four months, 80 per cent. Despite the fact that tuberculin 1:10 was used, only moderately intense reactions were obtained. There is a marked contrast in the duration of the preallergic postvaccinal period between young adult and newborn. After one month 85.7 per cent of the young adults were sensitive to the Mantoux test with 1:100 Old Tuberculin, whereas, four months were necessary to obtain the same result with a dilution of 1:10 in the newborn. The authors believe that this is due to the fact that water is more readily absorbed in the skin of the newborn than it is in the adult. In order to produce a local irritation, it is necessary for the tuberculin to remain a certain time within the skin. If the absorption time for fluid is accelerated, the tuberculin passes rapidly into the blood-stream. For that reason, the local reaction in the newborn

is less severe. The authors come to the conclusion that nothing shows that the immunity conferred by BCG is established after a prolonged period of time. Although the local allergy against tuberculin is retarded in babies they believe in effect that the Mantoux test does not give any indication as to the beginning nor to the intensity of the immunity. As practical consequence, there is no reason to isolate the vaccinated infants until the allergy appears.—*Influencia de la edad, color y grado del pilosidad sobre el comienzo de la sensibilidad tuberculinica. Post-vacunacion con B.C.G., R. A. Vaccarezza & C. A. Urquijo, Rev. argent. de tuberc., July–September, 1944, 10: 185.*—(*W. Swienty*)

Pathological Changes following BCG Vaccination.—The study is based on autopsies of 57 children up to the age of 2 who had received BCG vaccine and had died of nontuberculous diseases (bronchopneumonia, meningitis, dyspepsia, etc.). Twenty-five nonvaccinated cases were taken as controls. The entire group of vaccinated children showed characteristic changes in the reticuloendothelial system. The changes differed with the age of the child, being dependent on the time elapsed since vaccination. The lymph nodes showed a very pronounced catarrhal sinusitis. There was marked hyperemia. The lymph sinuses were dilated and filled with large endothelial cells and lymphoblasts. There was complete absence of monocytes and histocytes. The lungs showed accumulations of lymphoid and histocytic elements in the interstitial tissue of the cortical regions. The liver showed cellular infiltrates, mostly perivascular, consisting mainly of lymphocytes and occasional endothelial cells. In the spleen there was hyperplasia of the follicles and proliferation of endothelial cells in the sinuses. At the age of 6 months a quieting-down of all these processes was noted. The sinuses of spleen and lymph nodes became narrower, there was a regression of cellular infiltrations and a steady increase in histocytic elements at the site of the lesions. At the age of one year the lymph nodes showed progressive fibrosis. Spleen and liver revealed at this time analogous trends of cell metamorphosis. At the age of 2 all above processes were stabilized to a great extent. The lymphoid system showed the development of a fine fibrous tissue, especially in the marginal sinuses. The investigations show that reactions to the strain of BCG appear as early as a few weeks after vaccination, increase in intensity up to the age of 3 to 4 months, after which time retrogressive changes are observed, finally resulting in fibrosis after the age of one year. In addition to the above described reactions of "paraspecific" nature, 14 of the 57 children showed caseous lesions in the lymph nodes, combined in 3 cases with typical tubercle formation in the parenchymatous organs. Caseous lymphadenitis affected as a rule not less than 3 groups of lymph nodes. The order of frequency and intensity of involvement was: the cervical group, the submandibular group and the retropharyngeal group. The lymph nodes at the bifurcation and the tracheobronchial lymph nodes seemed to be involved to a minor extent, the lesions being less of the caseous and more of the paraspecific catarrhal type. Because of these findings it is supposed that the first changes after oral administration of BCG occur via the lymphatics of mouth and pharynx. This assumption is corroborated by the fact that in 3 cases specific tubercles were found in the tonsils. The paraspecific processes, occurring in all children, and the caseous lesions are considered as essentially related, differing only in the degree of reactivity of the reticulo-endothelial system towards BCG. The control group of unvaccinated children did not reveal any similar pathological findings. The 57 cases had received the BCG strain "Paris." Clinical observation had showed that administration of this strain had been followed by a higher incidence of clinical complications than the administration of the strain BCG I. A second pathological study was based on 20 autopsies of cases vaccinated with the BCG I. No fundamental difference in the reactions to the two strains was noted. Both produced an irrita-

tion of the reticulo-endothelial system. However, the reactions to the second strain were much less intense and less frequent. In addition, the delay after which retrogressive changes occurred was shorter, the onset of fibrosis being noticeable already at the age of 6 months. The incidence of specific changes with caseation and giant-cell formation was much lower; only one case out of 20. (Caseous mesenteric lymphadenitis.) This second group of autopsies showed the predominant changes in the lymphatic apparatus of the intestinal tract.—*Pathological Changes in Children Vaccinated with B.C.G., V. I. Pusik, Probl. tuberk., 1944, 5: 25.*—(*V. Leites*)

Vaccination with BCG.—In U.S.S.R. vaccination with BCG is conducted on a mass scale, being administered to the majority of newborn children. In 1940 635,000 children were vaccinated, in 1941 470,000. This investigation regarding the effectiveness of BCG was based on the study of children born in 1938. The first group consisted of 56,951 children who had been vaccinated at birth. The second group consisted of 17,469 children who had not been vaccinated for various reasons, mostly because of lack of vaccine. It was found that the mortality from tuberculosis within the first year of life was almost twice as high in the nonvaccinated group. This group also showed a higher morbidity from tuberculosis within the first year. The decrease in the mortality from childhood tuberculosis in Moskow has been about 40 per cent from 1937 till 1940. This decrease is considered by the author as an indirect proof for the effectiveness of antituberculous vaccination on a mass scale. Comparison of mortality rates from childhood tuberculosis in Moskow and Leningrad showed the greater effectiveness of subcutaneous vaccination which had been practiced in Leningrad. However, the difference was only slight, and it is not felt to warrant mass application of subcutaneous vaccination in the newborn because of the possibility of subcutaneous infiltrates.—*The Effectiveness of Anti-tuberculous Mass Vaccination with BCG, M. A. Klebanow, Probl. tuberk., 1944, 5: 48.*—(*V. Leites*)

BCG Vaccination in America.—Approximately 1,000,000 children were inoculated with BCG vaccine in Brazil between 1927 and 1942. In the same period 58,000 children were vaccinated in Uruguay and about 90,000 in Argentina. Various studies on BCG vaccination were made also in the U.S.A. The great majority of the vaccinated children became tuberculin reactors. Studies on rather small series of individuals, but under particularly favorable experimental conditions (identical conditions of life and of exposure), show markedly reduced morbidity and mortality rates among vaccinated children as compared to those found among not vaccinated controls. The statistical data obtained in the above countries are tabulated and the results tested by the method of Pearson. It appears that the markedly lower morbidity and mortality rates in vaccinated children as compared to suitable controls cannot be due to mere chance; they are rather a confirmation of the value of the Calmette Guérin method of prophylaxis.—*Analisis estadistico de los resultados de la vaccinacion antituberculosa con el B.C.G. en las Americas, A. P. Leon, Rev. mex. de tuberc., April, 1944, 6: 81.*—(*L. Molnar*)

BCG and Resistance to Tuberculosis.—The author has had twenty years of experience in Cuba with BCG vaccine. This experience has clarified some of the more obscure points regarding the action of BCG. Although the hopes of Calmette and his collaborators that the vaccine would result in a complete resistance to the infection did not materialize, it is now established that BCG is very efficient in augmenting resistance. But we do not yet know the exact mechanism of its action. A review of the literature shows that the observers who have had experience of at least 10,000 vaccinations are fervent partisans of BCG, whereas those who have had little experience generally are not.

Poor results have been obtained because of faulty technique or faulty preparation and handling of the vaccine. This was the case in Lübeck. The failures in obtaining a durable resistance are due mostly to using dead bacilli or products derived from dead bacilli. It is important that live germs be used. Dead BCG does not give any resistance, or for a very short period of time only. This has been proved by animal experiments. The author has studied the changes which take place as a result of the different manipulations during the preparation of the vaccine. The optimum for obtaining a good vaccine is a culture of less than twenty-eight days of growth on glycerine-potatoes at a temperature of 98.6°F. Trituration for thirty minutes with glass balls does not alter the vitality of the germs, but should not be maintained for more than fifteen minutes. It is questionable whether the natural primary infection is a process which should be imitated or improved by vaccination with BCG. The natural primary infection generally augments the resistance to reinfections, but can also cause a progressive infection with acute illness and even death. Immunity and allergy are expressions of the balance of different factors which intervene in the organic functions. Their equilibrium is necessary for the normal development of the organism and adaption to the new conditions that are created by any illness. In the phenomenon of Koch immunity reacts with the corresponding allergy. A direct action of the toxic substance exists with the specific antibodies. Subjects who have had glandular manifestations of tuberculosis in infancy have a greater resistance to the severe types of tuberculosis in later years. Two great mechanisms work together in the fight against the bacilli: the localization and destruction caused by the immunity, and the elimination. The action of the BCG has been explained as follows: The vaccine produces substances which act upon the newly arriving bacilli. The allergy is one of the phenomena of the immunization and expresses the degree of resistance. Successfully vaccinated persons should present an allergic reaction. The end of the immunization can be determined by the moment when allergy disappears. The vaccination should provoke early, intense and lasting allergy. The author's experiments with animals prove that we can no more consider allergy as a true expression of an improved resistance to tuberculosis. The BCG permits the discovery of anergy to tuberculin and certain modifications of an actual allergy. This may be called occult or latent allergy. Little is known of the mechanisms that take place in the prevention and curing of tuberculosis. In the beginning of the infection antibodies appear in the blood, and a more or less apparent allergy becomes evident. This is not an indication of healing or failure of healing. BCG vaccination is one form to normalize the primary infection by a non-dangerous mechanism. The establishment of allergy in a vaccinated subject without clinical evidence of tuberculosis can be interpreted as due to the vaccination. The author has experimented with an extract of BCG which is more active and less susceptible. Animal experiments with it have proved that the reaction to this extract is much more intense and lasting than with any other tuberculin. Systematic intracutaneous revaccination must be made independently of the allergization of the subject. This is necessary in order to maintain the immune reaction on a high level and to obtain a specific prophylaxis to tuberculosis. The author's BCG extract gives a high percentage of positive reactions in subjects who have not shown allergy after vaccination with PPD and OT.—*Sobre el aumento de la resistencia antituberculosa conferido por el B. C. G., P. Domingo, Rev. cubana de tuberc., July–September, 1944, 8: 411.*—(*W. Swienty*)

Pneumothorax.—The indications for induction of pneumothorax have become so elastic that the number of absolute contraindications (congestive heart failure, rapidly progressive bilateral disease, poor general condition, etc.) is small. Once pneumothorax is induced proper spacing of refills, observa-

tion of the status of the contralateral lung, frequent fluoroscopy and roentgenoscopy are some of the physician's responsibilities. Large pleural effusion, rupture of the lung, adherent pleuritis may, but not necessarily will, render the continuation of pneumothorax treatment impossible. Inadequate collapse is dangerous to the patient and to the community, and constitutes an indication for discontinuation of pneumothorax.—*Artificial Pneumothorax Treatment and Its Responsibilities, P. L. Deshmukh, Med. Bull., Talegaon Tuberculosis Sanatorium, Poona, India, November, 1943, 11: 1.*—(*P. Lowy*)

Pneumothorax.—The contraindications to artificial pneumothorax treatment are the following: (*1*) myocardial inefficiency, (*2*) dyspnea, (*3*) cyanosis, (*4*) extensive infiltration of both lungs, (*5*) emphysema, (*6*) hypertension, (*7*) advanced tuberculosis of other organs, except the larynx, (*8*) miliary tuberculosis, (*9*) advanced nephritis and (*10*) tuberculous pneumonia. Adhesions, obliterative pleuritis, purulent effusion, severe reactions after refills, perforation of the lung may necessitate discontinuation of pneumothorax treatment. Even if technically satisfactory collapse is obtained, the lesions may not heal and spread of the disease may occur. One hundred and eleven cases treated by the author were divided into three classes: (*1*) cases with unilateral disease, (*2*) bilateral tuberculosis with only one lobe affected in one of the lungs, (*3*) extensive involvement of both lungs. In only 10 (32 per cent) cases of the first group could effective pneumothorax be maintained. Fifteen (62.5 per cent) patients of the second class received pneumothorax treatment, and in only one of them was the treatment successful. In the third group no effective pneumothorax could be given.—*Limitations of Artificial Pneumothorax Treatment, P. L. Deshmukh, Medical Bulletin, Talegaon Tuberculosis Sanatorium, Poona, India, November, 1942, 10: 1.*—(*P. Lowy*)

Empyema and Pneumonolysis.—During a five-year period between 1938 and 1943, 754 sections of pleural adhesions were performed in the tuberculosis services of the city of Buenos Aires. Empyema occurred in 24 cases, of which 9 were related directly to the operation. In 5 of the 9 cases pulmonary perforation was the evident cause of the empyema. Four causes of perforation are listed: partial section of adhesions, cortical pulmonary lesions, bronchopulmonary hypertension from ball-valve mechanisms and the rupture of a zone of least resistance in the cauterized area.—*Consideraciones sobre empiema y operación de Jacobaeus, F. A. Médici & R. Sampietro, An. Cáted. de pat. y clin. tuberc., December, 1943, 5: 324.*—(*R. Kegel*)

Mediastinal Shift.—An inspiratory shift of the mediastinum toward the side of a pneumothorax may be observed sometimes. This shift is due to a disturbance of the equilibrium between intrapulmonary and intrapleural pressures. These pressures have been studied simultaneously in a guinea pig and it appears that during inspiration the intrapulmonary pressure descends to about −1.5 cm. of water and rises to +2 cm. of water during expiration. The intrapleural pressure changes from −7 cm. during inspiration to −1 cm. during expiration. Comparison of these two pressures reveals that the decrease of the intrapleural pressure is more pronounced than that of the intrapulmonary pressure. In other words, the difference between intrapulmonary and intrapleural pressure increases during inspiration and reaches a maximum shortly after the inspiration is completed. Thus, in the animal studied, the intrapulmonary pressure was 2.5 cm. of water higher than the intrapleural pressure during expiration, whereas the difference became 5 cm. of water shortly after inspiration. The mediastinal shift is due to the increased intrapulmonary pressure of the healthy lung during inspiration. When the pressure equilibrium is restored, the mediastinum returns to its normal position due to its own elastic retraction and to that of the healthy lung and not to an increase in the intrapleural pressure on the pneumothorax side. A mediastinal shift

occurs only under two conditions: (*1*) When the collapsed lung has lost all of its expansile capacity because the disease has progressed too far. (If only one healthy lobe remains, the inspiratory expansion of this healthy lobe is sufficient to overcome the disproportionately increased negative intrapleural pressure and no mediastinal shift occurs.) (*2*) When the mediastinum has become too flaccid due to too great refills and is pushed over toward the healthy side. In this case the mediastinum returns toward its normal position during inspiration and is again pulled toward the healthy side during expiration. A mediastinal shift indicates faulty technique in the management of a pneumothorax and often is due to too copious refills. Sometimes, however, it is difficult to prevent an inspiratory shift of the mediastinum in the case of a left pneumothorax because the heart, freed from the attraction toward the chest wall, tends to assume a median position due to its own weight. It results that, whereas in a right pneumothorax it is safe to arrive at a maximal intrapleural expiratory pressure of 0 or +1, it is safer never to surpass expiratory intrapleural pressure of −2 or −1 on the left, because "one must always jealously watch that in the course of a pneumothorax the mediastinum may not become deviated."—*Le balancement du médiastin au cours du pneumothorax artificiel, M. Baillet, Presse méd., May, 1940, No. 46, 525.*—(*G. Simmons*)

Spontaneous Pneumothorax in Infant.—An 18-day-old girl developed spontaneous pneumothorax followed shortly thereafter by staphylococcus empyema. Aspiration of air and fluid improved her condition, but it was necessary to perform rib resection and tube drainage to effect a cure. The infant was also treated with sulfathiazole, lavage of the pleural cavity and with transfusions. It is believed that the patient had developed a staphylococcus infection in her lung, and a subpleural focus ruptured into the pleural cavity. This assumption is strengthened by the fact that lavage fluid was coughed up on one occasion.—*Spontaneous Pneumothorax and Staphylococcal Empyema, Elizabeth Lund, Lancet, May 26, 1945, 248: 661.*—(*H. Marcus*)

Circulation Time in Bilateral Pneumothorax.—Mention is made of the various attempts to measure circulation time in collapsed lungs and the conflicting results obtained. The authors present their findings in 15 cases of bilateral pneumothorax. The arm-lung tract method of Hitzig (ether) in which four to eight seconds is considered normal, and the arm-tongue tract method of Winternitz, Deutsch and Bruell (decholin) in which nine to sixteen seconds is considered normal, were used. Circulation time was found to be normal in 12 of the 15 by the arm-lung tract method and in all by the second method. The authors found no relationship between circulation time and vital capacity. Consideration is given to the hyperemia and ischemia theories of the collapsed lung and the concept presented that both are compatible with pulmonary physiology. This, they claim, is possible because of the two types of blood vessels in the lungs, described by Tiemann and Daiber: one, the large repository vessels which may be full or empty (thus producing a state of hyperemia or ischemia), and the second, which surround the first and has a normal circulation.—*El tiempo circulatorio en individuos sometidos a neumotorax bilateral, N. Gonzalez de V. & J. Navajas T., Rev. españ. de tuberc., February, 1945, 14: 111.*—(*J. S. Peterson*)

Bronchospirometry in Pnemuothorax.—Spirometric tests were made on 13 cases of pulmonary tuberculosis, treated with unilateral pneumothorax. In the collapsed lung, a constant decrease of the vital capacity was noticed; a less marked decrease of the respiratory volume was also observed. The decrease of the vital capacity, in almost all cases, was chiefly due to the decrease of reserve air, and secondly to the decrease of the complementary air. The average decrease of the various percentages is 15.2 in the case of the vital capacity, 12.4 for the complementary air,

19.8 for the reserve air and 12.1 for the respiratory volume. The oxygen intake also decreased in the collapsed lung, especially in the cases complicated with atelectasis. The ventilation equivalent improves with the induction of pneumothorax. As regards the uncollapsed lung, a compensatory increase of the oxygen intake as well as the respiratory volume was recorded.—*Estudio broncoespirométricos en la colapsoterapia, R. F. Vaccarezza & A. Soubrié, An. Cáted. de pat. y clin. tuberc., June, 1944, 5: 5.*—*(H. Behm)*

Sodium Citrate as Preventive of Pleural Adhesions.—In order to prevent the premature loss of a pneumothorax space after the appearance of a pleural effusion 3.8 per cent sodium citrate was successfully used. In 44 cases of 5 to 6 years old pneumothoraces with small effusions, 5 cc. of 3.8 per cent sodium citrate solution was injected into the pleural space twice weekly for two to three months. Symphysis of the pleurae occurred only in 11 cases. Applying this method, the author succeeded in maintaining a good pneumothorax in 21 out of 25 cases of massive pleural effusion. The following technique is suggested: As soon as the pleural effusion sets in, 5 cc. of the solution are injected. This injection is repeated a week later and is repeated until the formation of fluid stops.—*Le citrate de soude moyen de lutte contre la symphyse pleurale, A. Dussert, Rev. de la tuberc., 1942, 7: 155.*—*(G. Simmons)*

Preoperative Cardiovascular Examination.—Circulatory complications which can interfere in thoracic surgery depend upon the sufficiency of the heart and its resistance to the surgical shock. In La Esperanza Sanatorium in Habana, Cuba, the patients scheduled for thoracic surgery go through a routine procedure of cardiovascular examinations which includes electrocardiogram, vital capacity and velocity of blood. Tachycardia is common in tuberculous patients. A pulse rate of more than 120 per minute over a prolonged period of time is the expression of a toxemic state of the myocardium and constitutes an absolute contraindication for any surgical intervention. A second stage thoracoplasty should be postponed if tachycardia intervenes after the first stage. The tachycardia may not only be the expression of a compensatory mechanism, especially if the hematopoiesis has been affected by extensive lesions or an exaggerated therapeutic collapse. If the arterial pressure is low the patient's general condition should first be built up. Hypotension is due to active vasoparesis and even dilatation of the arterioles as a consequence of the action of the tuberculous toxins on the vasomotor centres. Caution is advocated in case of hypertension. No patient with a blood-pressure of over 150 mm. Hg should be operated upon. The pleuropulmonary tuberculosis as well as all forms of collapse therapy seem to have no effect on the venous pressure. Among the large number of surgical cases at La Esperanza, not one has been observed with elevated venous pressure or collateral venous circulation after surgery. The venous pressure can only be affected by compression of the great veins, by tumor masses of the mediastinum, aortic aneurysm, enlargement of the lymph nodes of the axilla etc. These conditions may cause compression or obstruction of the lumen of the large veins. The value of the vital capacity tests is limited as the normal lung tissue of the patients is reduced by the pulmonary lesions or by the therapeutic collapse. Also, the tests have to be made on patients on absolute bed-rest or restricted activity. Changes in the heart great enough to produce changes in the electrocardiogram are not frequently seen in tuberculous patients, the most frequent being sinus tachycardia. This is caused by the action of the toxins on the autonomic centres of the heart and on the neurovegetative system, or by a hyperfunction of the adrenal gland. Other lesions visible in the electrocardiogram are rare. But myocardial lesions of tuberculous or nonspecific origin are frequently found in autopsies, although these lesions had not been seen in the electrocardiogram. Sinus tachycardia, if under 120 and not constant, and isolated extrasystoles are

no contraindications for surgery. Any tachycardia of over 120, frequent extrasystoles, electrocardiographic evidence of myocardial damage, heart block, auricular flutter, coronary occlusion are absolute contraindications. If chest surgery absolutely has to be done under these circumstances, local anesthesia should be used after controlling the toxemia as much as possible.—*Examen cardiovascular preoperatorio de los tuberculosos pulmonares en cirugia pulmonar, R. C. Barrena, Rev. cubana de tuberc., July-September, 1944, 8: 482.*—(*W. Swienty*)

Late Results of Thoracoplasty.—Of 242 cases of pulmonary tuberculosis treated with thoracoplasty, 20 (8.26 per cent) showed recurrence of the disease after "a long period of time" following the operation. In 17 cases the disease appeared on the side operated on. In 7 the recurrence was due to a too limited thoracoplasty and in 10 cases the thoracic wall was too rigid to permit a satisfactory collapse. In 3 cases there was recurrence of the disease on the contralateral side. Only 2 patients died. They had been operated on in 1929 and 1933, respectively, with an inadequate technique. Recurrences became manifest anywhere between seven months and eight years after the operation.—*Rechutes tardives de tuberculoses cavitaires unilatérales apparemment guéries par thoracoplasties, A. Bemon, H. Fruchand & M. Gautier, Presse méd., April, 1940, No. 33-34, 366.*—(*G. Simmons*)

Artificial Fibrosis.—The possibility of inducing pulmonary sclerosis with the use of different chemical substances was studied experimentally in dogs. Silver nitrate and torium bioxide are inadequate, because these substances are rapidly eliminated through the open bronchi. Various silicates mixed with collodion induce noteworthy sclerosis in the lungs of dogs. Best results, however, were obtained with a mixture of animal coal, cheratin (5:1) and collodion. This fluid mixture, introduced into the lung by means of a syringe, solidifies readily, adheres to the tissues and remains there, almost unchanged indefinitely. Around this substance a productive inflammatory process sets in, without secondary damage to lung tissue taking place. —*Sulla reazione del tessuto polmonare alla introduzione di sostanze estranee: Contributo sperimentale allo studio della chiusura artificiale di residui cavitari con bronco aperto nell'aspirazione endocavitaria, M. Mesiti & A. Baffoni, Ann. Ist. Carlo Forlanini, 1942, 6: 417.*—(*G. Simmons*)

Artificial Occlusion of Bronchi.—Lipiodol studies on cavities treated according to Monaldi's method of endocavitary aspiration revealed that in the majority of cases a residual cavity and open bronchi leading into the cavity persist after the treatment was discontinued, because clinically and radiologically the cavity had disappeared. The persistence of these residual cavities and bronchi is held responsible for the many failures to obtain permanent results with Monaldi's method. It was therefore thought to introduce a substance into the residual cavity which would be able to occlude permanently bronchus and residual cavity. Several substances (talcum, magnesium silicate etc.) were used unsuccessfully, but finally good results were obtained with a mixture of animal coal, cheratin and collodion. Numerous complications were encountered in the course of such a procedure: Sometimes there is a general reaction, which, however, is of short duration. The substance may be coughed up and bronchial irritation characterized by increased cough and mucous sputum may persist for some time. The substance may remain in the cavity and act like a foreign body, thus causing increased exudation and a filling-up of the cavity which had been believed closed following endocavitary aspiration. A reflow of the substance through the tract previously occupied by the catheter may occur, followed by pain, inflammation and formation of a fistula. Despite these facts, good results were obtained in several cases, but no definite statement as to the permanency of such cavity closures is at-

tempted at the present time, because the period of observation (six months to one year) and the number of cases are insufficient. In conclusion, it is believed that the theoretical approach to the problem, consisting in the necessity of occluding residual cavities and the distal part of bronchi leading into such a cavity with a substance which remains *in situ* permanently and causes a local sclerotic reaction, is correct, but that the substances used so far are not entirely satisfactory for this purpose.—*Tentativi di chiusura dei bronchi di drenaggio delle caverne applicati al metodo di aspirazione endocavitaria, V. Monaldi, Ann. Ist. Carlo Forlanini, 1942, 6: 403.*—(*G. Simmons*)

Artificial Occlusion of Bronchi.—Small residual cavities and the bronchus leading thereto were occluded successfully in 2 patients with a mixture of magnesium silicate and collodion, following Monaldi's intracavitary aspiration. No favorable results were obtained in other patients, because the substance, introduced by means of a catheter through the thoracic wall, was coughed up. A mixture of magnesium silicate and aluminum silicate (1:1) in collodion was subsequently used for the same purpose in 65 cases, and good results were obtained in about 50 per cent of the cases thus treated; 4 of them are described in the present paper. In the remaining cases different complications were encountered: filling-up of the cavity, which radiologically had appeared to be closed, with the substance introduced; activation of pericavitary nodular foci; secondary infection of the cavity; infection of the transthoracic tract which contained the catheter through which the intracavitary aspiration and introduction of the therapeutic mixture were practiced; pulmonary hemorrhages. None of the cases died, but the subsequent treatment, consisting in further intracavitary aspiration, was very long. In 60 other cases the closure of the residual cavity was attempted with the introduction of a mixture of animal coal, cheratin (5:1) in collodion. Although the occluding effect of this substance is inferior to that of the silicate mixture, the complications were fewer and a greater percentage of favorable results was obtained. Best results were obtained in cases in which there were no pericavitary tuberculous foci, the capacity of the residual cavity was not greater than 1 to 3 cc., the walls of the cavity were clean and when there was only a minimal amount of drainage.—*La chiusura artificiale delle vie bronchiali di drenaggio delle caverne nell'aspirazione endocavitaria.—Prime applicazioni cliniche, M. Mesili & A. Baffoni, Ann. Ist. Carlo Forlanini, 1942, 6: 439.*—(*G. Simmons*)

The Cavity Complex.—The authors have reviewed 3,000 cases of pulmonary tuberculosis; 71.93 per cent presented clinical and X-ray evidence of cavitation. The three factors which contribute to the cavitary complex are the break in continuity of the parenchyma, that is, the cavity itself, the condition of the surrounding parenchyma and the condition of the communicating bronchus. The size of the cavity during life often does not correspond to the real size found at autopsy. This difference depends not only upon size and location of the cavity, but also upon elasticity, tension and movement of the surrounding parenchyma. The surrounding lung tissue may be apparently healthy. In this case, the cavity presents a punched-out picture. It may be exudative and form an early infiltration. In case of primary specific fibrosis or secondary nonspecific sclerosis of the parenchyma, the X-ray film shows dense shadows surrounding the cavity. Pneumothorax will not reduce the size of the cavity to a great extent. The cavities are rigid. Atelectasis or emphysema are consecutive to the condition of the bronchus. The communicating bronchial tract may be stenosed by scars, by ulcers or by vegetations. The stenosis from scars generally does not produce complete obliteration of the bronchus, whereas ulcerations create a diminution of the bronchial lumen and subsequently an obliteration of the valvular type. The valvular mechanism may permit

the free passage of air during inspiration only, creating an intraälveolar hypertension in the pulmonary tissue which appears distended. The more the passage of air is obstructed during expiration, the greater the emphysema. The cavity becomes distended and increases in size. The reverse mechanism results in atelectasis and a decrease of the size of the cavity. The authors emphasize the widest use of the bronchoscope. If in the absence of clinical and X-ray findings tubercle bacilli are present in the sputum, bronchoscopy is always indicated. Bronchial lesions respond only to local treatment. The indiscriminate institution of artificial pneumothorax in the case of bronchial tuberculosis is often detrimental.—*El complejo cavitario en la tuberculosis del pulmon, R. Bellesteros S. & J. Aedo Blasco, Rev. cubana de tuberc., October–December, 1944, 8: 559.*—*(W. Swienty)*

Intracavitary Pressures.—By photokymography the authors recorded simultaneous tracings of intracavitary pressures and the respiratory excursions of the thorax. According to the pressures found, cavities were classified as normo-, hypo-, hyper- and inert, pressure cavities.—*Las presiones intracavitarias en la fisiopatologiá de las cavernas y su registro gráfico, O. Vaccarezza & L. Berlin, An. Câted. de pat. y clin. tuberc., December, 1943, 5: 336.*—*(R. Kegel)*

Valvular Drainage of Insufflated Cavities.—A 19 year old male underwent a thoracoplasty with a view to collapsing a cavity of the right apex. Satisfactory results were not obtained. Later a cavernotomy was performed with the resultant cure of the patient. Aspiration alone of the cavities without thoracoplasty does not yield good results. It is advisable first to perform a thoracoplasty, followed by drainage of the cavity approximately twenty days later. Intermittent aspirations are performed in the days subsequent to the drainage. A second thoracoplasty is performed in order to achieve complete collapse. Seventeen cases have been thus treated by the author with 55 per cent of permanent cure, one operative death, one death caused by acute edema of the lungs, 4 deaths due to the progress of the disease, and 3 patients are alive but still positive for tubercle bacilli. Eloesser's technique is described. A modification of this technique, devised by the author, consists in the approximation and suturing of the cut-surfaces of the skin. Eloesser's operation alone should not give results, unless combined with thoracoplasty. —*Drenagem valvular das cavernas pulmonares insufladas (operacao de Eloesser), A. Amorim, Rev. brasil. de tuberc., September–October, 1944, 95: 259.*—*(P. B. Franca)*

Intracavitary Aspiration.—The following abstract is based on four different papers, which contain basically the same facts and the same material, but were published at different times in different journals. The papers used were:

1: Versuche über den Verschluss der Drainagebronchien bei Anwendung des Verfahrens der Kavernensaugdrainage, V. Monaldi, Ztschr. f. Tuberk., 1942, *89:* 105.
2: Der gegenwärtige Stand des Kavernensaugdrainageverfahrens in der Behandlung der tuberkuloesen Lungenkavernen, V. Monaldi, Ergebn. d. inn. Med. u. Kinderh., 1942, *62:* 68.
3: L'aspirazione endocavitaria nelle sue attuali direttive pratiche, V. Monaldi, Medicina e Biologia, 1942, *1:* 253.
4: Die Kavernensaugdrainage in ihren theoretischen Grundlagen und in ihren klinischen Indikationen (Beobachtungen an 700 Fällen), V. Monaldi, Deutsche med. Wchnschr., 1942, *11:* 673.

Extensive bibliography, up to and including 1941, may be found in the papers mentioned under (2) and (3). Monaldi's method of intracavitary aspiration in the treatment of certain forms of pulmonary tuberculosis has been generally accepted and the fear of operative complications has proved to be unfounded. During the first 100 intracavitary aspirations Monaldi had one fatal pulmonary embolus during the insertion of the trocar,

and another one during the reinsertion of a catheter which previously had been expelled without the cavity having been completely closed. Considering that the operation has been performed about 1,000 times and reinsertion of a catheter has been done not less than 2,000 times, the two above cited cases and another one of transient embolus from which the patient recovered represent a negligible percentage of operative complications. Hemorrhages during the operation are equally rare and if they do occur during the process of aspiration sometimes may be controlled by introduction of a thin rubber balloon, mounted on the catheter, into the cavity. The balloon may be inflated and thus local hemostasis may be produced. Infection of the catheter-bed occurs only rarely and can readily be controlled by discontinuing the aspiration temporarily. Instead of using one of the recently developed apparatus, the author prefers the old-fashioned system of two bottles partly filled with water to obtain the negative pressure desired and reserves the use of higher negative pressures, such as may be obtained with different apparatus, for the use on cavities with rigid walls and those in which it is difficult to establish a negative intracavitary pressure on account of widely patent bronchi. Too high and too prolonged suction is said to disturb the biological equilibrium, thus facilitating hemorrhages and exudative processes. By using the two-bottle system, the pressure varies continuously with the changes in the water level. The catheter can be introduced even in small-sized cavities with or without the aid of certain apparatus, such as those designed by Morelli or Dorn and Cadeddu. The author uses a trocar whose calibre corresponds to a No. 9 Nélaton catheter. It is admitted that cavities with initially and permanently occluded bronchi at the completion of the intracavitary aspiration are exceptions. As a rule, after the disappearance of the cavity following Monaldi's procedure, the bronchus leading into the "occluded" cavity remains open. To obtain a permanent closure of the communicating bronchus, experiments with the introduction of different tamponading and sclerotizing substances, injected into the residual cavity and the corresponding bronchus, have been carried on since 1941. It is generally admitted that immediate beneficial effects are obtainable with the Monaldi procedure, but the author maintains that permanent cures, too, may be obtained if the indications for this treatment are followed and if the treatment is carried out correctly. As causes for the reopening of cavities the following factors are considered: (*1*) The persistence of necrotic material in the cavity or the new formation of such material from small pericavitary foci which remained active. In this case the cavity walls touch each other, but permanent obliteration of the space does not occur. (*2*) Too early discontinuation of the treatment. In this case the walls touch each other but the time allowed for formation of scar tissue was not sufficient. (*3*) Persistence of a patent bronchus leading into the residual cavity. The author claims, on the basis of these considerations, that the majority of unsuccessful aspirations are due to faulty technique. The reduction of the volume of the cavity is only one factor in the process of healing, which in addition calls for: 1) cleaning of the cavity walls; 2) closure of the draining bronchus; 3) restitution of the anatomical and functional integrity of the pericavitary parenchyma; 4) stability of the newly formed scar tissues. Even though the cavity reopens, its further evolution is slowed down, the local and general condition of the patient is not compromised and the treatment can be resumed without difficulty. In conclusion and on the basis of his personal experience the author asserts that definite and permanent healing of cavities with the intracavitary aspiration may occur. As far as the indications for the Monaldi procedure are concerned, the problem of the origin of the cavity is considered. The method is contraindicated in the so-called "biological cavities" (fusion cavities) in which the loss of substance is great and the pericavitary tissue is diseased. But it is indicated in those cavities in whose formation mechanical factors, such as re-

traction of broken elastic fibres, were prevalent and which therefore are surrounded by atelectatic tissue. The author pleads for the abandonment of the conception of rigid cavities due to sclerotic phenomena and claims that the rigidity is only apparent and caused by the deposition of dense pathological material on the cavity walls. Once this material is eliminated, the walls become elastic again and may be subject to concentric retraction. Intracavitary aspiration therefore may be done even on very old cavities or those persistent after other collapse methods have failed. The method should not be used in partial or total fibrothoraces, however. Complete and persistent positive results were obtained also in cavities with a surrounding exudative process. Concomitant improvement of other homo- or contralateral lesions or concomitant diseases, such as diabetes, was observed, but not always. In brief here are the indications for the Monaldi procedure: (*1*) isolated cavities, surrounded by healthy lung tissue; (*2*) stationary cavities with inactive disease in the surrounding tissues; (*3*) pluricavitary lesions, as long as they fit into one of the above mentioned categories. In the presence of several cavities, the Monaldi procedure may be used in the following conditions: (*1*) isolated and separate bilateral cavities; (*2*) multiple cavities in the same lung, separate and distant from each other; (*3*) two cavities close together, of which at least one must be small and surrounded by considerable amount of healthy lung tissue; (*4*) communicating cavities. In the case listed under (*4*) the aspiration of one may close both cavities. In the case listed under (*3*) the same result may be obtained by applying suction to the superior cavity. In all other cases multiple aspirations are necessary. The author does not give any statistical material, but refers to "150 cases which had pulmonary tuberculosis for from three to fifteen years and which are cured or are near to being cured." Case histories and X-ray films of 31 patients with excellent results are reported. To obtain permanent closure of the draining bronchus after the completion of the intracavitary aspiration the author injects, after visualization of the residual cavity and the bronchus, a mixture of charcoal and cheratin (5:1), dissolved in collodion, into the residual cavity. The catheter is removed after an hour. This method was introduced in 1941 after experiments on dogs, sacrificed at intervals varying from a few hours to six months after such a treatment had proved that the substance injected becomes thick, adherent to the tissues and finally surrounded by fibrous tissue. Complications are encountered occasionally (coughing-up of substance injected, elimination through the catheter sinus, reopening of the cavity, exudative reaction etc.) but as a whole the results are considered to be very satisfactory, although, again, no statistical material is given. X-ray films of 5 cases in whom occlusion of the bronchus was artificially produced are reproduced in the paper listed under (*1*). The operative and postoperative technique is given in detail in the paper listed under (*2*).—(*G. Simmons*)

Pulmonary Hemorrhages during Intracavitary Aspiration.—Pulmonary hemorrhages, including streaking, occur not infrequently in the course of intracavitary aspiration. They were studied in 700 cases in which Monaldi's treatment was applied. In cases in which the bleeding was due exclusively to the therapeutic procedure, the following causes were most frequently found: (*1*) operative trauma and consequent injury to vessels of the lung or the thoracic wall; (*2*) too great negative pressure applied to the cavity; (*3*) temporary occlusion of the bronchus leading into the cavity due to the patient's position with consequently rising negative intracavitary pressure; (*4*) the catheter being in contact with the cavitary wall causes a local inflammation with new formation of vessels and their subsequent rupture. The treatment of these hemorrhages is subordinate to the cause and consists essentially in a temporary suspension of the intracavitary aspiration, the adjustment of the position of the tip of the catheter etc. In some cases,

however, in which the bleeding was particularly persistent local hemostasis with the introduction of a small rubber balloon into the cavity was successfully performed. The catheter was removed, the balloon was introduced into the cavity and inflated to the desired size. Thus local pressure was exerted on the interior surface of the cavity. No unfavorable reactions were encountered and the balloon was removed after five to ten days.—*Sul trattamento di alcuni fenomeni emorragici nel corso dell'aspirazione endocavitaria. M. Maselli & S. Chiodi. Ann. Ist. Carlo Forlanini, 1942, 6: 515.*—(*G. Simmons*)

Reopening of Cavities after Intracavitary Aspiration.—Since the reopening of cavities after the completion of intracavitary aspiration and the radiological disappearance of the cavity is a common experience, apparently closed cavities were filled with lipiodol and the draining bronchus could be invariably demonstrated. It is clear, therefore, that the resistance offered by the bronchi is much greater than that of the cavity in itself. It is believed that the negative pressure used during the intracavitary aspiration is not sufficient to cause collapse of the bronchial walls. Furthermore, during those periods of intracavitary aspiration during which suction is not applied (at night, at mealtime etc.) the artificially created negative pressure in the cavity causes an influx of air through the partially collapsed bronchus and restitution of the original size of the cavity. Since attempts of occluding the bronchus leading into the cavity by means of introduction of blood, electrocoagulation etc. were not successful, it is suggested to obtain a permanent collapse of the bronchus leading into the cavity by means of a permanent very highly negative pressure. The negative pressures used were as high as 60 to 90 Hg/mm. No details about the length of such a treatment and the results obtained are given.—*Die Wiedereröffnung ausgesaugter Kavernen und ihre Verhütung. L. Kiss. Ztschr. f. Tuberk. 1942, 89: 11.*—(*G. Simmons*)

Pneumonectomy for Primary Tuberculous Pneumonia.—A 5½ year old boy was referred to surgery with the diagnosis of gangrene of the right lung. During the operation large areas of caseation were found in the lung. The diagnosis of "primary caseous necrotic gangrenous tuberculous lobitis" was established and later proved by bacteriological studies. A great part of the lung was removed. The patient was cured and has remained so for nearly six years.—*Lobite tuberculosa primaria caseo-necrotica gangrenosa, pulmonectomia e cura. A. Amorim, Rev. brasil. de tuberc., July–August, 1941, 94: 197.*—(*P. B. Franco*)

Technique of Lobectomy.—Barnia states that his experience has shown him that the site of the incision for the extirpation of the different lobes must not only follow anatomical reasons but depends also on the nature of the underlying pathological process. Lobectomies for cancer in which there are no or few adhesions should be guided by anatomical reasons, the pulmonary or lobar pedicle determining the incision. In case of pulmonary suppuration with frequent adhesions, the incision should be made where the adhesions can most easily be freed. Always, the lobe has to be freed first. After that the pulmonary vein or its ramifications are ligated and cut. Next comes the artery and last the bronchus. There is no more bleeding from adhesions when they are freed before or after the vessels have been tied. For the left upper lobectomy the antero-median two-thirds of the fifth rib are resected and the fourth rib cut near the postero-lateral extremity of the incision. The possibility of a special vein for the lingula has to be kept in mind. After dividing, the bronchus is closed after Rienhoff. The bronchial stump is covered with pleura or a portion of the parenchyma. For the inferior left lobectomy, the sixth rib is resected, either totally or in its posterior two-thirds; for the superior right lobectomy, the fourth rib in its anterior two-thirds; for the right middle lobectomy, the

anterior two-thirds of the fifth rib; and for the inferior right lobectomy, the sixth rib entirely or its posterior two-thirds. In this case the author uses the lateral portion of the middle lobe to cover the bronchial stump. Before closure of the thorax the remaining lobes are inflated by the anesthetist. Failure to distend fully and freely is considered as proof of injury. The noninflated segments should be resected at once.—*Tecnica de las lobectomias pulmonaras, R. Barata R., Rev. cubana de tuberc., October–December, 1944, 8: 637.—(W. Swienty)*

Rapid Growth of Mycobacteria.—Rapid and submerged growth was produced by five strains of saprophytic mycobacteria, five virulent avian strains, one bovine strain (Ravenel) and two human strains (H37RV and Jamaica No. 22) on Long's medium to which was added (*a*) phosphatide fractions prepared from egg yolk, cattle brain, human erythrocytes and soya bean, (*b*) synthetic non-ionic surface active agents consisting of esters of long chain fatty acids and of polyhydric alcohols. Addition of 0.1 cc. of culture to 10 cc. of new medium was sufficient to secure growth of the saprophytic and avian strains within twenty-four hours and of the bovine and human strains within seventy-two hours. Addition of purified serum albumin (0.1 per cent or less) further enhanced the growth. The cultures so obtained were typical in morphology and staining characteristics and grew slowly again and on the surface when returned to Long's medium.—*Rapid and Submerged Growth of Mycobacteria in Liquid Media, R. J. Dubos, Proc. Soc. Exper. Biol. & Med., April, 1945, 58: 361.—(F. B. Seibert)*

Hamster versus Guinea Pig for Tuberculosis Diagnosis.—To find a test animal for the presence of tubercle bacilli which would be more economical than the guinea pig would be of definite value. It has been suggested that the hamster, a small Asiatic rodent, might replace the guinea pig for biological tuberculosis tests because of its low cost and maintenance, its smallness (economy of space), short gestation period (sixteen days with litters of 6 to 10), and its susceptibility to inoculation tuberculosis. The earliest report on the use of hamsters in the diagnosis of tuberculosis appears to be that by Korns and Lu from Peking Union Medical College in 1927. They found them cheap and quite sensitive to injection tuberculosis, although the lesions were smaller than in the guinea pig and there was less caseation. On the other hand, tubercle bacilli are usually found in abundance in the lesions, an advantage over the guinea pig where they are sometimes difficult to find. These authors made no comparison of the hamster's susceptibility to tuberculosis with that of the guinea pig, so doses were not standardized. Nevertheless, they concluded that the hamster was a practical substitute for the guinea pig. Two other investigators also reported that the hamster was suitable for the diagnosis of tuberculosis, but rather large doses of organisms were used in their experiments. Since all available data contain no accurate information as to the actual susceptibility of the hamster as compared with the guinea pig, the present authors decided to determine this by quantitative experiments. There seem to be two hamsters extant, namely the Syrian or golden hamster and the striped hamster. These resemble each other very closely. The former was used. Three human and two bovine strains of virulent tubercle bacilli were employed. Hamsters and guinea pigs in turn were injected subcutaneously each with 1.0 mg. or 0.001 or 0.000,001 mg. of the different strains of bacilli. The guinea pigs were found to be definitely more susceptible to tuberculosis than the hamsters for all showed involvement, even after the smallest dose, whereas it nearly always took the largest dose to produce any involvement in the hamsters. One of the bovine strains however, a eugonic strain (the other was dysgonic), did produce some tuberculosis with the smallest dose in the hamsters, but

the involvement was not quite as great as in the guinea pigs. It is evident that the guinea pig, relatively speaking, is far more susceptible to virulent human tubercle bacilli injected subcutaneously than is the hamster. For this reason the guinea pig is the animal of choice for the clinical diagnosis of tuberculosis. The superiority of the guinea pig over the hamster in this wise is not as great when bovine tuberculosis is being considered. The article ends with a plea for the use of cultural methods for detecting bacilli instead of by injection although no definite data are presented illustrating the advantages of the former. (Illustrated.)—*The Biological Diagnosis of Tuberculosis: Quantitative Animal Evaluation Tests on the Syrian Hamster and the Guinea Pig, H. J. Corper & M. L. Cohn, Am. J. Clin. Path., November, 1944, 14: 571.—(J. S. Woolley)*

Gastric Examinations.—The author emphasizes the importance of the examination of gastric washings for the etiological diagnosis of pulmonary tuberculosis. He refers to the difficulties of obtaining sputum in children and adults who do not expectorate. He mentions the fact that in some countries the material obtained from the bronchial tree by bronchoscopy is examined instead of the gastric washings. The question whether the bacilli found in the gastric washings are of pulmonary origin and whether they originate from active lesions is discussed. The author states that in the great majority of cases the bacilli found in the gastric washings are of pulmonary origin and come from active lesions. The concepts of "open and closed" pulmonary tuberculosis, "normal carriers" of tuberculous bacilli are to-day considered obsolete. Under the medico-social point of view the examination of the gastric washings is as important as roentgenological examination. The author describes in detail the technique he uses for the examination of the gastric washings. This includes the culture in Loewenstein asparagine medium and guinea pig inoculation.—*O lavado gastrico e sua importancia medico-social, H. E. Jouval, Rev. brasil de tuberc., May-June, 1944, 93: 155.—(P. B. Franca)*

Diagnostic Pulmonary Lavage.—The search for tubercle bacilli in the bronchial lavage was tried in tuberculous patients who could not raise sputum. After applying local anesthesia to the pharynx and trachea, 20 to 40 cc. of saline solution were instilled in the bronchial tree, and the material thus coughed out was collected. Nineteen positive cases, by smear, culture, or guinea pig inoculation, were found in 80 completely investigated cases. These patients either produced no sputum, or the sputum examination had been negative. A comparative study between the results of the examination of the pulmonary lavage and the gastric lavage was made in 12 patients, both tests being made the same day. Whereas no positive case was found in gastric lavage examinations, tubercle bacilli were found in 5 cases in pulmonary lavage examinations.—*Primeiros resultados do lavado pulmonar no diagnostico bacteriologico da tuberculose, M. Abreu, Ap. respir. y tuberc. (Chile), January-March, 1945, 10: 5.—(H. Behm)*

Diagnostic Pulmonary Lavage.—The intercrico-thyroid puncture for pulmonary lavage has been abandoned. The author devised a new transglottic method. The uvula, pharynx, larynx and trachea are anesthetized with 0.5 per cent novotutocaine solution; 20 to 40 cc. of physiological saline solution are then introduced during inspiration. Cough is provoked and the secretion is collected for examination. To reach all parts of the lung the patient is instructed to move his chest in all directions. This method of pulmonary lavage has been used in all cases of suspected pulmonary tuberculosis without cough or expectoration and in which sputum and gastric contents are negative for tubercle bacilli. One hundred and seventy lavages were done. The method is well tolerated, even in patients with hypertension. No case of dissemination of the disease has been observed. This is due to the fact that hematogenous and bronchogenic spreads depend

upon the same immunological and biological factors which are responsible for clinical progression. In 3 cases with chronic bronchitis slight elevation of temperature for one day was observed. In 80 lavages enough material was obtained for culture and animal inoculation. Of these, 19 were found to be positive. In all 19, previous sputum and gastric examinations had always been negative. Direct microscopic examination of the specimen was positive in only 3 cases, whereas the culture was positive in 12 and animal inoculation in the remaining 4. Lately the author has not used more than 10 cc. of saline solution. Sometimes even the 4 cc. of novotutocaine are enough to produce sufficient secretion. An average of 10 lavages a day are now done in the two main hospitals of Rio de Janeiro, Brazil.—*El lavado pulmonar en el diagnostico bacteriologico de la tuberculosis, M. D. Abreu, Prensa méd. argent., March 9, 1945, 32: 405.—(W. Swienty)*

Detection of Tubercle Bacilli in Urine.—The author examined 443 twenty-four-hour urine specimens which were preserved by addition of 1.5 ml. one per cent acriflavine (3,6 diamino, 10 methyl acridine chloride) and 40 ml. McIlvaine's buffer solution pH 4.0. The urine was precipitated by addition of 5 ml. 5 per cent tannic acid, refrigerated overnight and then centrifuged. The precipitate was digested at 37°C. for twenty to thirty minutes with 3 per cent sodium hydroxide, washed with physiological saline. Smears were made and Petragnani's medium inoculated and incubated at 37°C. Colonies of *M. tuberculosis* appear after two weeks and within four weeks. Acid-fast bacilli were found in 10.8 per cent of the smears while 16.6 per cent of the cultures were positive for *M. tuberculosis;* however, 6 of the positive cultures originated with concentrates found negative by smear. The author reports that the collection of urine in the acriflavine-buffer solution inhibits the growth of other bacteria frequently present in specimens from cases of renal tuberculosis. The concentration of acriflavine used exerts no effect on *M. tuberculosis.—Routine Examination of Urine for Mycobacterium Tuberculosis, H. J. Peppler & J. T. Hill, Brit. J. Exper. Path., December, 1944, 25: 193.—(H. J. Henderson)*

Tubercle Bacilli in Pleural Fluid.—Great divergence exists in the literature as to the frequency of tubercle bacilli in pleural fluids (Frederiksen, 1934, 5 per cent; Naito, 1938, 82 per cent). Using different culture media the pleural fluid of 63 patients with primary pleurisy with effusion was examined and positive bacteriological results were obtained in 58, 33 per cent. Noteworthy is the fact that the fluid of several patients in whom the effusion was obviously due to tuberculosis and who died of this disease shortly afterwards was negative for tubercle bacilli.—*Presenza del bacillo di Koch nell'essudato delle pleuriti siero-fibrinose cosidette primitive, G. Daddi & G. Spina, Ann. Ist. Carlo Forlanini, 1942, 6: 196.—(G. Simmons)*

Tubercle Bacilli in Milk.—Tuberculin tests were made on 322 cows in Buenos Aires. These tests showed a percentage of tuberculous infection as high as 30.7 per cent. Tubercle bacilli were investigated through smears and guinea pig inoculations in 94 samples taken from the allergic cows showing no symptoms of tuberculous mastitis. No tubercle bacilli were found in any of the samples. This investigation, nevertheless, cannot be considered as final, in view of the fact that the bacteriological research was not complete, and only one guinea pig inoculation was made in each case. The negative results seem to be particularly influenced by the absence of tuberculous mastitis. Special emphasis was placed on the danger of such wide-spread tuberculous infection among cows, which brings forth the possibility that at any moment a tuberculous mastitis could break out, thus contaminating the milk.—*Investigación del bacilo de Koch en la leche de vacas tuberculino-positivas, A. R. Arena & R. Cucchiani, An. Cáted. de pat. y clin. tuberc., June, 1944, 5: 68.—(H. Behm)*

Rapid Staining of Acid-fast Bacilli.—Rapid routine staining of acid-fast organisms with

carbolfuchsin usually employs heat to produce more rapid penetration of the stain. Recently Tergitol No. 7, a detergent or wetting agent, was used as a substitute for heat and found that staining occurs more rapidly than with heat. One drop of Tergitol is added to 30 to 40 cc. of Kinyoun's carbolfuchsin prior to use. Smears are stained for one minute and sections of tissue for five minutes followed by decolorization with acid alcohol and counterstaining as usual. The shorter time required for staining and the ease with which the procedure can be employed constitute improvements in technique which make the methods particularly applicable to routine use. Equal or better results are obtained with these procedures than with the older methods, and none of the required specificity for acid-fast organisms is lost.—*A Rapid Staining Technique for Acid-fast Organisms, H. E. Mueller & R. L. Chermock, J. Lab. & Clin. Med., February, 1945, 30: 169.—(F. G. Petrik)*

Demonstration of Tubercle Bacilli in Sputum.—A comparative study was made of four methods used to prepare sputa for the identification of tubercle bacilli. The methods chosen were (*1*) direct smear, (*2*) autoclave (heat coagulation) and concentration, (*3*) sodium hydroxide digestion and concentration, and (*4*) clorox digestion and concentration. The results show that the clorox digestion method is the most efficient. With it, the greatest percentage of positive specimens was obtained and there was a greater concentration of organisms per microscopic field. Because of this greater concentration fewer fields had to be examined to find acid-fast bacilli.—*Comparison of Methods Adaptable to Production Line Examination of Sputum for Tubercle Bacilli, G. M. Cameron & R. Castles, J. Lab. & Clin. Med., February, 1945, 30: 163.—(F. G. Petrik)*

Alveolar Cells of Lung.—The nature of the cells lining the air sacs, the subject of many investigations in the past (Villemin, Zenker, Kölliker, Addison), has been revived in recent years by investigators who used modern histo-physiological methods. Opinion is divided between those who state that the pulmonary alveoli are lined by a continuous layer of epithelial (ectodermal) cells and those who found that the walls of the alveoli are virtually "nude" and that cells found scattered along the septa are mesodermal. Porto's study is concerned with the structure of the lower respiratory portion of the lung, particularly with the cells lining the walls of the air vesicles. The experiments were conducted on dogs, cats, rabbits and rats who received trypan blue via the trachea. Experimental procedures as well as methods used in the study of the material are given in some detail. The conclusion was reached that morphologically, by their disposition and functions, the cells of the septa are of mesodermal origin and that they are a part of the macrophage (reticulo-endothelial) system of Metchnikoff. Porto failed to find so-called anucleated plates along the septa, but he disclosed the presence of interalveolar communications (pores of Kohn) which, in his view, is another evidence against the epithelial nature of the cells "lining" the pulmonary septa.—*The Nature of the Alveolar Cells of the Lungs, J. Porto, Publicaciones del centro de investigationes tisiologicas, Buenos Aires, vol. 7, p. 349.—(B. M. Fried)*

Erythrocyte Sedimentation Rate.—The only safe and sound solution of the problem of "correction" of values for the sedimentation rate is to discard all correction charts and to evaluate the observed sedimentation rate by comparison with the clinical picture, since one knows from a large body of statistics how the sedimentation rate is usually affected in different diseases. Recording of degrees of sedimentation at frequent intervals is only time-consuming and gives no more information than a reading at the end of one hour. Determinations of the sedimentation rate need no longer be omitted if venipuncture is not practicable, since a pipet can be made which is suitable for both venous and capillary blood. A long pipet is far preferable to a short

one. Normal and pathological values of the sedimentation rate are practically the same whether obtained with the Westergren pipet, which is 2.5 mm. in diameter, or with a long pipet 1.2 mm. in diameter which permits the use of either venous or capillary blood. Thus one may profit from statistics compiled from millions of readings made with the Westergren pipet. (Author's Summary.)—*Determination of Sedimentation Rate of Red Blood Cells: Use of So-Called Correction Charts and Optimum Length and Diameter of the Pipet, J. T. Peters, Arch. Int. Med., February, 1945, 75: 105.*—*(G. C. Leiner)*

Endobronchial Tuberculosis.—Endobronchial tuberculosis complicates the treatment of pulmonary tuberculosis and increases the gravity of the prognosis. It may occur at any stage of parenchymal disease. There is a fairly high incidence in minimal cases. Failure to apply present knowledge results in a high incidence of complications in collapse procedures applied to patients with tuberculous bronchitis. These are then considered therapeutic failures with persistent positive sputum, uncontrolled symptoms, empyema, unexpandable lung, atelectasis and anaerobic infection. Endobronchial tuberculosis has been found in 10 to 15 per cent of patients at the time of sanatorium admission. An incidence of 30 to 60 per cent is reached in those with symptoms or signs. There is a preponderance of females, 75 to 85 per cent in the literature, and 72 per cent in the series reported by Wilson. Twelve per cent of the children admitted to Maybury Sanatorium present the clinical picture of "epituberculosis" at some time or other; 75 per cent of these give bronchoscopic evidence of endobronchial tuberculosis or bronchial occlusion due to involvement of lymph nodes. Forty per cent of tuberculosis autopsies reveal endobronchial tuberculosis. The earliest lesion seen bronchoscopically as well as pathologically is submucosal, representing an extension to the main bronchus from a bronchial division. The posterior half of the bronchus is more frequently involved than is the anterior half. Later, hyperplastic changes with ulceration are seen. Healing by fibrosis may occur at any stage and may produce stenosis. Stenosis is most likely to occur in areas involved by extensive ulceration or by hyperplastic changes. In 36 consecutive cases of stenosis there were 20, or 55.5 per cent, involving the left main bronchus and 11, or 35.5 per cent, involving the orifice of the right upper lobe. The explanation for this predilection is unknown but may be concerned with lymphatic drainage in the bronchial wall. Clinical indications for bronchoscopy consist in unilateral wheeze, positive sputum without evidence of parenchymal source, severe symptoms without evident parenchymal source, intermittent retention of secretions or prolonged fever following thoracoplasty are indications for bronchoscopy. Roentgenologically, mediastinal shift with or without elevation of the diaphragm, "hilar flare," opaque lesions appearing suddenly following institution of collapse therapy, basal tuberculosis, certain types of cavity (thin-walled, those containing fluid levels, those that fluctuate in size), wide-spread parenchymal disease without evident parenchymal source, and obstructive emphysema are indications for bronchoscopy. The following contraindications to bronchoscopy are listed: terminal tuberculosis, pulmonary hemorrhage, acute respiratory infection and acute tuberculous laryngitis. Bronchoscopic technique is stressed as of the utmost importance. Three grains sodium pentobarbital and $\frac{1}{6}$ grain morphine are given in preparation together with local anesthesia consisting of 10 per cent cocaine hydrochloride to the posterior pharynx and 2 per cent to the trachea and bronchi. The bronchoscope should be passed slowly and kept proximal to the lesions. Granulation tissue or ulcerated areas should receive applications of 30 per cent silver nitrate. The bronchoscope should be withdrawn slowly with aspiration of secretions accumulating around the tube. After bronchosopy, to avoid spread, the patient should lie on the affected side for three hours since the cough reflex has been abolished.

Results obtained by therapy depend on (*1*) the type of endobronchial lesion, the submucosal lesion having better prognosis than have the others, (*2*) the interval between treatments (a two to three week interval should be maximal or granulation tissue grows up causing stagnation of secretions and increased inflammatory reactions), (*3*) the general therapy being administered, (*4*) the duration of bronchial disease, and (*5*) the control obtained of parenchymal lesions. The author advises that no attempt be made to dilate fibrotic stenosis. Instead he suggests thoracoplasty or pneumonectomy. He advises against biopsy because of the possibility of initiating ulceration. He advises treatment with silver nitrate every two weeks until healing ensues, following which intervals between applications should be gradually lengthened. If no response is obtained over a reasonable time pulmonary resection is advised.—*Bronchoscopic Observations in Tuberculous Tracheobronchitis—Clinical and Pathological Correlations, N. J. Wilson, Dis. of Chest, January–February, 1945, 11: 36.* —(*K. R. Boucot*)

Tuberculous Bronchopathy.—A case of residual tuberculous bronchiectasis is described. The etiological factors for residual tuberculous bronchiectasis are: constitutional debility of the wall of the bronchus, altered tension caused by the infection and the retention of the secretion, peribronchitis, tuberculous lesion of the bronchial wall, artificial collapse and pleural effusion which during reabsorption causes a lowering of the intrathoracic pressure. In a second case, a bronchial obstruction was found in a woman of 33 years of age who had had asthma since she was two years old which disappeared after puberty and reappeared with her first pregnancy. She had been exposed during her infancy to direct tuberculous contact. It is thought that the reappearance of the asthma during pregnancy is due to the reactivation of the childhood lesions. At this time the clinical symptoms of bronchial obstruction started. The pathogenesis is explained as follows: pregnancy and childbearing as anergic causes; exogenous reinfection; aspiration; lysis and absorption of the bacilli by the lymphatics; endogenous reinfection and softening of the tubercle. Bronchoscopy was negative for tuberculous lesions but the sputum was highly positive. Repeated X-ray studies gave the picture of a slowly progressing atelectasis of the left lower lobe. A lipiodol study showed almost complete obstruction of the secondary and tertiary bronchi. This case is considered as a proliferative tuberculous bronchitis with localization in the finer bronchi of the left inferior lobe. Incidentally, it was found that the patient had narrowed bronchi of the right lower lobe, probably as a sequela of congenital syphilis which may have been the predisposing cause for the subsequent tuberculous localization.—*Broncopatias cronicas tuberculosas, H. G. Machado & A. C. Mendez, Rev. cubana de tuberc., July–September, 1944, 8: 486.*—(*W. Swienty*)

THE

AMERICAN REVIEW OF TUBERCULOSIS

ABSTRACTS

VOLUME LIII FEBRUARY, 1946 ABST. NO. 2

Bronchoscopy.—Originally, the bronchoscope was devised for the removal of foreign bodies; to-day, bronchoscopy is an important supplemental method in the diagnosis and treatment of bronchopulmonary diseases. Its chief indications are hemoptysis, thoracic tumors, lung abscess, asthma, tuberculosis, bronchial obstruction and bronchiectasis. In certain conditions (heart disease, aortic aneurysm, pulmonary embolism, emphysema, bronchopneumonia, inflammatory lesions of the larynx, etc.) bronchoscopy is contraindicated or else not sufficiently informative. In 106 cases of hemoptysis in which X-ray examination was negative, bronchoscopy revealed the cause of the bleeding; in 34 additional cases bronchoscopy, too, was negative. The diagnosis of thoracic neoplasms has been greatly furthered by the use of bronchoscopy. Unfortunately, the suspicion of malignancy frequently arises too late for surgical treatment; hemoptysis is usually a late symptom. In 75 per cent of all tumor cases bronchoscopy leads to the correct diagnosis and it makes the differentiation and removal of benign tumors possible. In lung abscess, drainage can be promoted and the extent of the abscess determined by bronchoscopy. Many cases of lung abscess could be prevented if patients who vomited during an operation were immediately bronchoscoped. In some instances, bronchial asthma refractory to medication may be benefited by the removal of tenacious secretions. Preoperative bronchoscopy is indicated in pulmonary tuberculosis in order to exclude tracheobronchial lesions. Following surgical treatment, the bronchoscopist may be able to find the cause of persistent positive sputum. Bronchial obstruction of whatever cause calls for bronchoscopy, both as a diagnostic and as a therapeutic procedure.—*The Diagnostic and Therapeutic Possibilities of Bronchoscopy, G. J. Taquino, New Orleans M. & S. J., January, 1945, 97: 291.—(P. Lowy)*

Treatment of Tuberculous Bronchitis.—Local treatment with a 10 to 15 per cent solution of silver nitrate is advocated for nonstenotic tuberculous bronchial lesions occurring in the course of pulmonary tuberculosis. For disease refractory to bronchoscopic treatments or in stenotic bronchial lesions, collapse therapy is advised, thoracoplasty if the condition of the patient permits, pneumothorax being the second choice. Phrenic nerve operations are contraindicated. When the bronchus to the middle or lower lobe is involved, lobectomy may be considered in place of thoracoplasty. Occasionally cavitary drainage may be attempted.—*El tratamiento de la tuberculosis pulmonar con bronquitis tuberculosa asociada, R. Vaccarezza & A. Bence, An. Cáted. de pat. y clin. tuberc., December, 1943, 5: 263.—(R. Kegel)*

Tuberculous Empyema.—Among 4,527 patients with pulmonary tuberculosis treated in the Buenos Aires tuberculosis services between 1938 and 1943 there were 53 cases of tuberculous empyema, an incidence of 1.1 per cent. Of these 53 cases, 11 occurred spontaneously during the course of pulmonary tuberculosis, 42 arose during a therapeutic pneumothorax and 6 followed pneumonolysis. The incidence of empyema in 1,332

patients with pneumothorax was 3.1 per cent and in 513 with pneumonolysis 1.1 per cent. Broncopleural fistula was found in 68 per cent of the patients with empyema. Three clinical forms of empyema are recognizable, the simple, the toxemic and the malign. The last two are subdivided into pure and mixed infections. The kind of treatment depends upon several factors: the empyema itself, the status of contralateral or homolateral pulmonary lesions and the general condition of the patient. Medical treatment, aspirations and lavage, is tried first with thoracotomy and thoracoplasty in reserve. Of 39 patients treated, favorable results were obtained in 11 (28 per cent). There were 5 cures, 3 by thoracoplasty and one each by aspiration and by lavage. Seven patients were unimproved and 21 (54 per cent) died.—*Empiema pleural tuberculoso, J. Peroncini, R. Cucchiani & J. Niemetz, An. Cáted. de pat. y clin. tuberc., December, 1943, 5: 298.—(R. Kegel)*

Surgery of Tuberculous Empyema.—Since 9 of 10 patients with tuberculous empyema ultimately require one or another form of tuberculous intervention, the surgeon should be consulted at the onset of the disease so that the most favorable time for surgical treatment may not be missed. Early operations obviate the concomitants of late empyema, namely pachypleuritis and amyloidosis. In simple empyemata medical treatment, including aspiration and lavage, rarely cures empyemata. For aspirations a curved-aspirator inserted under fluoroscopic control is advocated. The patient should not be considered cured while an internal fistula is present. Most empyemata require an initial thoracotomy followed by a plastic operation. —*Consideraciones quirúrgicas sobre el empiema pleural tuberculoso, O. Vaccarezza, An Cáted. de pat. y clin. tuberc., December, 1943, 5: 310.—(R. Kegel)*

Tuberculous Meningitis.—Authentic cases of recovery from tuberculous meningitis are rare. A 16 year old boy became ill with typical clinical meningitis. Tubercle bacilli were demonstrated in his spinal fluid on smear and on culture. He made a complete recovery and was well seventeen months after the illness. The isolated bacilli were tested further and proved to be human tubercle bacilli of low virulence by animal inoculation. The second patient was a 41 year old woman in whom the diagnosis of tuberculous meningitis was made on the grounds of clinical meningitis and the finding of tubercle bacilli on smear and culture. Unfortunately the organisms were not tested as to their type and virulence and the patient was lost sight of.—*Recovery from Tuberculous Meningitis, G. H. Jennings, Lancet, April 14, 1945, 248: 466.—(H. Marcus)*

Meningoencephalitis in Hutinel's Disease. —A case of Hutinel's disease (pericardial and perihepatic symphysis) is reported. The interesting features in this case were the absence of free ascites and of liver cirrhosis and the rather rare complication of a meningoencephalitis in the right fronto-parietal lobe, accounted for clinically by a left-sided hemiplegia and paralysis of the facial nerve of the central type. The absence of liver cirrhosis can be explained by the cerebral complication occurring in the course of a generalized hematogenous dissemination, that terminated the life of the patient before a cirrhosis could develop. The nature of the cerebral localization proved to be tuberculous by the finding of numerous tubercle bacilli. Histologically there was only an acute nonspecific inflammatory process.—*Las complicaciones hemiplejicas meningoencephalicas de la enfermedad de Hutinel, P. H. Cantonnet, H. Lieutier, C. Perdomo, R. Radice, H. Castiglione & J. Medoc, Rev. de tuberc. d. Uruguay, 1944, 12: 73.—(L. Molnar)*

Tuberculin Sensitivity and Desensitization in Renal Tuberculosis.—The threshold of sensitivity to tuberculin was studied in a series of cases of genitourinary tuberculosis. The most reliable and safest method was found to be the one proposed by Liebermeister: sensitivity to tuberculin was tested start-

ing from the smallest dose of 0.1 cc. of a solution 1:1,000 billions, expressed as 10^{-16}, and using for successive tests doses ten times larger (10^{-15}, 10^{-14}, 10^{-13}, etc.). The sensitivity to tuberculin was determined in 50 cases of unilateral kidney tuberculosis before surgery, or bilateral disease, in which surgery was contraindicated; in 15 cases of kidney tuberculosis after nephrectomy and finally in 10 cases of different urological involvement. There was a marked hypersensitivity in all cases of kidney tuberculosis. Patients with a low sensitivity (for instance 10^{-3}) have, in general, a better prognosis than those who are hypersensitive (for instance 10^{-15}). It is usually not difficult to differentiate a case of hypoergy, indicating a favorable immunological condition, from another where the low degree of sensitivity is an indication of terminal failure of the immunological situation. Generalization of tuberculosis, following nephrectomy, may be due to bacillemia caused by manipulation of tuberculous tissues, or to the reactivation of latent foci as a result of a failure in the defense mechanisms provoked by the surgical trauma. The desensitization to tuberculin prior to surgery or following surgery could, theoretically, influence the incidence of postoperative generalization. The first step towards desensitization is the determination of the threshold of sensitivity to tuberculin. Then 0.1 cc. of the threshold dose is injected intracutaneously twice a week, using increasing doses (tenfold), after each dose has been tolerated without any local reaction. A similar but somewhat slower course of desensitization could be followed in inoperable (bilateral) kidney tuberculosis. The relatively small material and the short period of observation do not warrant definite conclusions as to the effectiveness of this procedure. Desensitization after nephrectomy was employed as an attempt to control a residual cystitis; the results were, however, very uneven. Desensitization may sometimes be impossible, as in cases of so-called "fixed allergy."—*Sensibilidad y desensibilización tuberculinicas en la tuberculòsis renal, L. C. Delatte & M. M. Diez, Rev. españ. de tuberc., October, 1944, 8: 744.*—(*L. Molnar*)

Genital Tuberculosis.—Genital tuberculosis is always a diffuse canalicular tuberculosis and a specific epididymitis is therefore nothing but the most easily detectable localization of a tuberculous process, secondary to a hematogenous, lymphatic or canalicular spread from the lungs or from the kidneys. That is why deeper lesions often persist after epididymectomy. They are not rare, but very often ignored. Biopsy of the testicle in cases of tuberculosis of the epididymis reveals almost constantly characteristic tuberculous lesions. Epididymectomy is not a radical operation but a palliative one and should not be performed until the process has become stabilized. It is only a precaution to prevent further extension and aggravation of the tuberculosis of the testicle. Epididymectomy should not be performed when the genital tuberculosis is a secondary phenomenon of a severe visceral tuberculosis, when the diagnosis is uncertain or when the disease is in its acute stage. The condition of the kidneys must always be investigated before epididymectomy is performed, because often tuberculosis of the kidney coexists and if nephrectomy is feasible, the genital tuberculosis often subsides after eradication of the renal focus.—*Remarques sur la tuberculose génitale de l'homme, B. Fey & R. Couvelaire, Presse méd., August, 1944, No. 15, 226.*—(*G. Simmons*)

Tuberculosis of Rectum.—Tuberculous lesions of the anorectal region are always a consequence of tuberculosis of other organs, generally the lungs. Infection takes place by swallowing of sputum containing bacilli. Occasionally the infection may be caused via the lymphatics or the blood. All anorectal fistulae and abscesses observed by the author have been of tuberculous origin; 19.69 per cent of all patients with pulmonary tuberculosis had some kind of rectal disease. Among 1,300 tuberculous patients, 75 (5.76 per cent) had fistulae, 43 (3.3 per cent) had

abscesses. The other 10 per cent had some form of nontuberculous disorder. Fistulae and abscesses are more frequently found between the ages of 18 and 42 years. The prognosis depends upon the development of the primary infection.—*Tuberculosis pulmonar y proctologia, R. Borlenghi, Rev. Asoc. méd. argent., February, 1945, 59: 91.*—(*W. Swienty*)

Vesico-intestinal Fistula.—Case history of a 21 year old male, who six months after the onset of a bilateral pleurisy with effusion developed abdominal pain, ascites and fever. The temperature decreased, but after three months rose again, the patient lost weight, had frequent diarrheas and nightsweats. The abdominal pain was recurrent and followed by a desire to urinate. Urination was painful and frequently interrupted by the emission of bubbles of gas. The urine had a fecal odor and tests for urobilin and indican were positive. Only traces of albumen were present. Fecal material was found in the urinary sediment. The patient died two and one half months later. (No autopsy.) It is assumed, however, that this patient had a specific intestinal ulcer which had ruptured into the bladder.—*Ein Fall von Darmtuberkulose mit einer Blasen-Darmfistel, S. A. Duursma, Nederl. tijdschr. v. geneesk., 1942, p. 140.*—(*G. Simmons*)

Tuberculosis of Myocardium.—This is a rare localization of tuberculosis. Generally it is secondary to tuberculosis of the pericardium or of the mediastinal lymph nodes. It may be caused by direct invasion by the blood-stream or by the lymphatics. Most often it is encountered in miliary tuberculosis. It then has no great prognostic importance because the myocardial process is only one manifestation of the wide-spread general infection. In the caseous form great parts of the heart muscles may be destroyed, but still there may not be any special symptoms which would allow making the correct diagnosis *in vivo*. The prognosis depends upon the development of the primary lesion and on the site of the lesion in the myocardium. The case of a 17 year old Negro boy, who had been suffering for three years of swellings of various joints, is discussed. Shortly before his admission he suffered from dyspnea, pain, palpitation and cough. The only cardiac sign was a soft blowing murmur in the fifth intercostal space to the left of the sternum. The X-ray film showed enlargement of the heart and congestion of the lungs. Blood cultures and agglutination tests were negative. The sedimentation rate was 43 mm. after one hour. The patient improved slightly on salicylates but died one month later with the symptoms of meningitis. The findings of the cerebrospinal fluid were not typical for tuberculous meningitis. The tentative diagnosis was purulent meningitis and mitral stenosis of rheumatic etiology. On autopsy, caseous tuberculosis of almost all the heart muscle was found. The patient had tuberculous meningitis and generalized miliary tuberculosis. The localization in the heart muscle was secondary to the involvement of the mediastinal lymph nodes, whereas the general hematogenous spread originated later from the cardiac lesion.—*Tuberculosis del miocardio, F. Saffie S. & R. Valenzuela Garcia, Rev. méd. de Chile, March, 1945, 73: 233.*—(*W. Swienty*)

Tuberculosis of Myocardium with Embolism.—A 65 year old white woman entered the hospital because of sudden nausea, vomiting, sweating, salivation, weakness. The heart was found enlarged, the electrocardiogram showed partial A-V block and intraventricular block. Signs and symptoms of occlusion of the right femoral artery and later of the left femoral artery appeared. The patient died. The autopsy showed marked chronic fibroplastic myocarditis; mural thrombosis of the endocardium of the left and right ventricles of the heart; cloudy swelling of the myocardium; embolism of the aorta, the right and left common iliac arteries, the right and left external and internal iliac arteries, and the right and the left femoral arteries; recent infarcts of the kidneys, spleen

and left lung; marked fibrous stenosis of the anterior descending branch of the left coronary artery; chronic fibrous tuberculosis of the lungs, calcification of the tracheobronchial lymph nodes and of the parabronchial lymph nodes and gangrene of both legs and feet. Microscopic examination of the lateral wall of the left ventricle showed masses of granulation tissue composed of epithelioid cells, lymphocytes and giant cells. Some of the giant cells contained refractile radial inclusions. These radial inclusions probably are a crystalline form of fat. Two structures closely simulating acid-fast bacilli were found in these lesions. Tuberculous myocarditis with endocardial thrombosis is not infrequent, but embolism from these thrombi is rare.—*Embolic Thrombosis of the Abdominal Aorta with Tuberculous (Histologic) Lesions of the Heart Containing Giant Cells with Radial Inclusions, R. A. Beebe & G. H. Coleman, Am. Heart J., April, 1945, 29: 539.—(G. C. Leiner)*

Tuberculosis of Eye.—Certain cases of keratitis and iritis, accompanied by cervical lymphadenitis, may be the expression of an allergic manifestation, inasfar as toxins from these tuberculous lymph nodes may maintain or reactivate intraocular tuberculous foci. Irradiation or surgical removal of these lymph nodes may result in spectacular cures. Five cases of keratitis are reported in which cervical radiotherapy led either to cure or to considerable improvement of the eye condition. Similarly, arthritic processes may be maintained by toxins or waste products from tuberculous lymph nodes. Thus, one patient, suffering from iritis and rheumatoid arthritis of the wrist and fingers and presenting enlarged cervical lymph nodes, was remarkably improved after institution of cervical radiotherapy.—*Le traitement des tuberculoses oculaires et rheumatismales par suppression de foyers ganglionnaires, J. Brun, Presse méd., April, 1943, No. 14, 180.—(G. Simmons)*

Tuberculosis of the Trochanter.—Tuberculosis of the greater trochantic bursa is rare and usually occurs secondary to osteomyelitis of the trochanter. Not until 1904 was concomitant involvement of the trochanter recognized. Later Cone and Swindt stressed the importance of trauma as an etiological factor. In subsequent series reported, the majority of cases showed evidence of healed or active tuberculosis elsewhere in the body. Complete removal of all infected tissue and immobilization of the affected part is the treatment of choice. Clinically, tuberculosis of the greater trochanter and its bursa is unusual in children but occurs at any age and in either sex. Usually there is mild pain in the involved leg over a long period of time with intervals of quiescence. A history of trauma may precede the onset of symptoms. There is slight swelling over the trochantic area, tenderness on pressure, but, as a rule, no pain on weight-bearing. Hip motion is free. Often a draining sinus is present over the trochantic area. Recurrences are common, some showing extension of the disease. The first X-ray evidence may be a small fleck of calcium in the bursa or a minimal area of destruction in the outermost part of the trochanter. The usual X-ray bone technique may not reveal the lesion. Therefore, Donovan and Sosman recommend the soft-tissue technique used to demonstrate calcium around the shoulder. The usual roentgenological finding in long standing cases is an area of destruction in the great trochanter with osteoporosis of the adjacent bone and some soft tissue swelling with calcium deposits in the bursa. Tuberculous involvement of the bursa must be differentiated from simple inflammatory bursitis which presents more acute symptoms and responds to simple treatment. Involvement of the trochanter requires differentiation from tumors and nonspecific osteomyelitis. Four cases of tuberculosis of the trochanter and its bursa are presented.—*Tuberculosis of the Greater Trochanter and Its Bursa, P. C. Briede, Radiology, January, 1945, 44: 32.—(G. F. Mitchell)*

Ultraviolet Radiation Control of Airborne Infection.—In the sleeping quarters of naval

recruits arranged in two groups of buildings of 11 each on both sides of a central training field, ultraviolet lamps of high and low intensity were installed in half of the buildings. The other half served as controls. Within these quarters a combination of upper air and floor irradiation was employed. The level of ultraviolet intensity was a determining factor in the control of airborne infection. A reduction of 25 per cent in respiratory illness resulted in those barracks equipped with high intensity radiation. There was no appreciable reduction in the rate of illness in the barracks equipped with low intensity irradiation. This reduction was most noticeable in the early winter months when the rate of illness was high throughout the camp. Bacterial counts in the irradiated quarters showed a 50 per cent reduction in the bacterial population of the air as compared with that in the nonirradiated control barracks.—*Ultraviolet Control of Air-borne Infections in a Naval Training Center, S. M. Wheeler, Lt. (MC) USNR, H. S. Ingraham, Lt. (MC) USNR, J. Gershon-Cohen, Lt. Comdr. (MC) USNR, & E. W. Brown, Capt. (MC) USN, Am. J. Pub. Health, May, 1945, 35: 457.*—*(M. B. Lurie)*

Pathology of Atypical Pneumonia.—The morbid anatomical changes in 42 cases from the U. S. Army of acute interstitial pneumonia (the so-called atypical pneumonia, etiology undetermined) are described. Of these, 21 were uncomplicated by superimposed secondary bacterial infection. The bronchioles revealed an acute focal bronchiolitis with early ulceration and, in some instances, complete desquamation of the mucous membrane. The bronchiolar lumina contained frank pus mixed with desquamated and disintegrated cells; no bacteria could be found in most cases. The walls of the bronchioles were dilated, sometimes markedly, even in the cases in which death occurred early, but complications such as chronic bronchiectasis were not seen and necrosis of the walls was seen in only one instance. The walls were infiltrated chiefly with mononuclear cells extending radially into the regional interstitial tissues of the lung, and in some cases there was fragmentation of the smooth muscle, elastic and reticulum fibres. The larger and medium sized bronchi showed only submucosal edema and congestion with a scattering of mononuclear and polymorphonuclear cells; focal ulceration was noted in only two instances. The alveolar walls were most severely involved close to the affected bronchioles; the lumina frequently contained air although focal areas of atelectasis were seen. In some instances there was extensive desquamation of alveolar lining cells and less frequently serous exudate with or without hyaline membrane formation. Usually no polymorphonuclear leucocytes were seen in these areas, and no microörganisms were found. Hemorrhages, when present, were usually terminal and were limited to those alveoli close to involved bronchioles. In the presence of secondary bacterial infection such as frank bronchopneumonia, lobar pneumonia and pulmonary abscess, it was sometimes possible to distinguish areas of acute interstitial pneumonitis in adjacent portions of the lung. The similarity of the lesions to those seen in measles pneumonitis and in epidemic influenza, especially when death occurs within the first five days of illness, together with the failure to demonstrate consistently any organisms in the lung tissue, suggests that a virus may be the etiological agent; it is pointed out, however, that acute interstitial pneumonitis is also seen in pertussis, a bacterial infection. In the cases in this series the leucocyte count tended to be high with 70 to 98 per cent polymorphonuclear cells; all of these cases came to autopsy, however. Cyanosis was common, and was best explained by the massive plugging of the smaller bronchial branches, the interstitial infiltration of alveolar walls and the pulmonary congestion. The presence of hyaline membranes was too inconstant to be the sole explanation.—*Pathologic Anatomy of "Atypical Pneumonia, Etiology Undetermined": Acute Interstitial Pneumonitis, A. Golden, Arch. Path., October, 1944, 38: 187.*—*(D. G. Freiman)*

Etiology of Atypical Pneumonia.—The present status of the etiology of primary atypical pneumonia is reviewed. A variety of known agents, including bacteria, fungi, Rickettsia and viruses, can produce this clinical syndrome, but accounts for a very small proportion of the cases diagnosed. The cause of the remainder remains to be identified. The results of extensive animal experimentation have been difficult to interpret owing to the lack of a truly susceptible animal and the occurrence of spontaneous diseases in the animals employed; there has as yet been no confirmed report of the isolation in animals of an agent definitely related immunologically to the human disease. The variety of immunological reactions demonstrable in convalescent sera, including cold hemagglutination, fixation of complement with various dissimilar antigens but especially fresh tissue suspensions, the prevention of the development of antibodies to the mouse pneumonia virus, and the agglutination of an indifferent streptococcus can be attributed to a nonspecific alteration in the serum proteins and their reactivity as well as by common antigens. Because of these equivocal findings, experiments were conducted with human volunteers. In the first experiment, sputa and throat washings from cases of atypical pneumonia were sprayed into the noses and throats of 12 men; of these, 2 failed to become ill, 2 developed mild infections without fever and 3 developed moderately severe atypical pneumonia. Between these extremes there were cases resembling the disease but without demonstrable pulmonary infiltration; these cases were similar to those diagnosed as "bronchitis resembling atypical pneumonia" or "suspected atypical pneumonia." In the second experiment 36 men were isolated, great precautions being taken to avoid cross infection and extraneous exposure. They were divided into three groups, the first being inoculated with 10 cc. each of pooled sputa and throat washings from 7 cases of atypical pneumonia, the second with a similar amount of this same material bacteriologically filtered, and the third with this same material autoclaved. All of the first group, 9 of the second and 4 of the third became ill either with primary atypical pneumonia or minor respiratory illness of undifferentiated type; however the cases of pneumonia were about equally distributed in all groups (3 in the first, 4 in the second and 3 in the third). No conclusion regarding infectivity of the filtrates could therefore be drawn and the question of nonspecific evocation of a latent agent or inadvertent infection was raised. The experiment was therefore repeated redoubling precautions against inadvertent infection and increasing the size of the control group receiving autoclaved sputum to 18. The inoculum now consisted of pooled sputa and washings obtained from 6 of the cases from the second experiment, thus providing an opportunity for passage of the agent On this occasion the results in groups one and two were the same, with 3 cases each of atypical pneumonia and 5 cases each of undifferentiated respiratory illness; 4 cases in each group failed to become ill. In the control group there was only one case of mild respiratory illness in a man known to have broken isolation; all the rest remained well. These results suggest that primary atypical pneumonia is initiated, if not caused by a filtrable agent, presumably a virus, and that a latent agent is not evoked nonspecifically. A difference in incubation periods, almost twice as long in those cases receiving filtered inoculum, suggests the possibility that bacteria may act in conjunction with the filtrable agent; the possibility that filtration causes some loss of the infecting agent cannot be ruled out however.—*The Present Status of the Etiology of Primary Atypical Pneumonia: Commission on Acute Respiratory Diseases, J. H. Dingle, Director, Bull. New York Acad. Med., May, 1945, 21: 235.*—*(D.G. Freiman)*

Atypical Pneumonia.—One hundred and forty-four cases of primary atypical pneumonia in ambulatory patients were studied. Pleural involvement was found in 21 patients (14.5 per cent), in 11 of whom no parenchymal lesion could be demonstrated. In only 3

cases was the site of the pleurisy the costophrenic sinus, while in the rest the pleuritic process involved the lower portion of one of the long fissures. The anatomy and roentgenology of the interlobar fissures are described and illustrated in detail. Clinically, the majority of the 144 patients had only mild, non-incapacitating symptoms (cough, slight expectoration, malaise, chilliness) and there was no difference, in this respect, between the patients with and without pleural involvement. Physical signs were scant and consisted of diminished or exaggerated breath sounds, slight dulness, subcrepitant and/or rhonchial râles and occasional pleural friction rub. The temperature, pulse, urine, leucocyte count and differential count were normal in most cases. Roentgenographic signs of pneumonia or pleurisy usually disappeared in two to four weeks. Involvement of the lower end of one of the long fissures presented itself in the frontal view as a small area of homogeneous density in the lower lung field extending down to the cardiophrenic angle and not reaching beyond the midclavicular line laterally. In the absence of pneumonia the lung markings were normal. In the lateral view, a band-like or fusiform density could be seen near the junction of the diaphragm and the anterior chest wall. In the oblique (right anterior for the left and left anterior for the right long fissure) films a homogeneous triangular shadow in the anterior portion of the lung field indicated involvement of the lower end of the interlobar fissure. In the differential diagnosis, pneumonia or atelectasis of the right middle lobe, pneumonia in the lower anteromedial portion of the left upper lobe, and infiltrations in the lower lobes must be excluded. Middle lobe pneumonia presents a triangular, and not a band-like, appearance in the lateral view. Pneumonic processes located in the lower medial portion of the left upper lobe do not extend down to the diaphragm in the postero-anterior film, while in the lateral view they show up as a broad area of density. Lower lobe infiltrations can be distinguished from interlobar pleurisy by the lesser homogeneity and posterior location of the former. The high incidence of pleural involvement in the authors' series of atypical pneumonias is partly attributed to the frequent use of lateral and oblique views.—*Pleuritic Involvement Associated with Primary Atypical Pneumonia: A Roentgenographic and Clinical Study, A. L. Bachman, N. O. Sara & H. E. Mantz, Am. J. Roentgenol., March, 1945, 53: 244.*—(*P. Lowy*)

Friedlander Bacillus Pneumonia. — The authors have compiled 287 cases of pneumonia caused by Friedlander bacillus from the entire world literature from 1882 to 1941; 233 of those with a mortality rate of 94 per cent were acute and 54 with a mortality of 30 per cent were chronic forms. (The cases of Zander (411) and Bathmagar and Singh (13) were disregarded as without exact control.) It is difficult to distinguish between the *Klebsiella*, *Echerichia* and *Aerobacter* groups. There even exist intermediatory forms between these different groups. The antigen contained in the capsule of *Klebsiella pneumoniae* type B, is similar to the capsule antigen of pneumococcus type 2. Although rare, some forms of *Klebsiella* can pass from the gram-negative to a gram-positive stage. Friedlander bacillus and all of the *Klebsiella* are habitual inhabitants of the respiratory system of man and it has been found that the localization in the tonsils is the most frequent. The authors have treated 244 cases of pneumonia of which 29 (11.8 per cent) were caused by *Klebsiella*. In 15 cases the pathogenic agent was *Klebsiella pneumoniae*. In 8 it was *Klebsiella ozaenae* and in 6, *Klebsiella capsulata*. All the germs were found in the sputum and the diagnosis was made only after at least six positive cultures were obtained. In 10 cases pneumococcus was associated with the *Klebsiella*, in 4 others, tubercle bacilli. Never was fungus found in association with the *Klebsiella*. The infection was always bronchogenic and generally started from the tonsils. Predisposing factors were colds, alcoholism, malnutrition, physical exhaustion and infection of the respiratory tract. Sixteen acute pneumonias and one

acute bronchopneumonia were studied. The acute form generally started abruptly. Herpes was rare. The patients were cyanotic and dyspneic. The age of the patients was from 18 to 64, with an average of 37.7 years. The mortality was 4 (25 per cent). Death occurred in ten to twenty-eight days. The average age of these patients was 48.8 years. Fifteen cases presented localization in the inferior lobes. Only one involved the upper left lobe. Fever and sputum were atypical. In 2 cases septicemia, purulent meningitis and pleuritis were found. Three cases showed leucopenia with shift to the left and monocytosis. Of 2 cases with lymphopenia, one died. Five had leucocytosis and shift to the left. Of those, 4 had monocytosis and one monocytopenia. Tubercle bacilli were not found in any one of the acute cases. The treatment consisted of sulfathiazole. In one case it was combined with penicillin. The duration of the disease was from five to thirty-seven days with an average of 17.7 days until full recovery. Twelve chronic forms were also studied. In 4 cases pneumococci and in 4 Koch bacilli were found associated with the Friedlander bacillus. The age was from 27 to 71 years with an average of 46.1. One 31 year old patient died sixteen months after onset of the disease. The start of the disease was abrupt in 7 and insidious in 5. The clinical picture is easily mistaken for tuberculosis. In 4 cases pulmonary abscesses were present. In 2 others tuberculous cavities appeared during the disease. Eight patients had leucocytosis with shift to the left; 5 of them had monocytosis. Four other patents had a normal white count. One patient recovered after forty-three days. All the others remained unchanged from three months to ten years. Death is generally due to toxemia. There is an intense reaction of the pulmonary tissue to this toxemia which is followed by necrosis and persistent pulmonary edema. Necrosis and hemorrhages are common in the acute forms. Bacteremia is almost always present in the acute forms of Friedlander pneumonia, but it is generally not followed by spread to other organs. For example, meningeal complications are rarely seen. The bacteremia has no prognostic significance. Relative or absolute leucopenia generally gives a poor prognosis. In the X-ray picture four different phases of the development of the disease can be seen: First, beginning bronchopneumonia; second, secondary pseudolobar coalescence; third, formation of multiple abscesses and thin walled cavities; fourth, fibrosis. In differential diagnosis of the acute forms pneumococcus pneumonia can be ruled out by the absence of herpes, the tendency to bilateral involvement, the abscess formation and the bacteriological examination of the sputum. Pulmonary gangrene also has to be excluded. Complications are pulmonary abscess, empyema, pleuritis, septicemia and meningitis. The chronic form has a relatively benign course over months or years. It often simulates pulmonary tuberculosis. The X-ray picture is always suspicious of tuberculosis, and association with tuberculosis is not infrequent. The cavities are thin-walled, and contain a purulent hemorrhagic fluid. The differential diagnosis has to exclude tuberculosis, chronic bronchitis, bronchiectasis and multiple lung abscesses. Complications are pulmonary abscess, empyema, bronchiectasis, hemoptysis, phlebitis, arthritis and endocarditis. The treatment in the acute and chronic forms consists of the sulfanilamides, good nutrition and rest. Penicillin seems to have no effect. The high percentage of recovery, especially of the acute forms, is due to the modern treatment.—*Neumopatias a Friedlander, F. Hermosilla D., S. Marin Tagle, L. Parades & E. Bellolio Z., Rev. méd. de Chile, January, 1945, 73: 36.*—(*W. Swienty*)

Treatment of Empyema.—More than 90 per cent of all the pneumococcal pneumonias are pleuro-pneumonias. Empyema generally appears when the disease is in the phase of grey hepatization. A portion of the parenchyma may soften and an abscess form. The evacuation of the pus may take place by vomica. But often the pus is evacuated into the pleural cavity, especially if not too

many adhesions are present. Generally, postpneumonic empyema is observed in patients who had no adequate medical care or who present a definite lowering of resistance towards the invading agent. In some cases, the empyema heals spontaneously by absorption or even by vomica. The empyema does not retard the healing of the parenchymatous lesions. Occasionally, it may extend and provoke mediastinal, subphrenic or pericardial abscesses. Therapeutically, it is of the utmost importance to avoid all maneuvers that could interfere with the respiratory equilibrium of the hemithorax. Surgical methods that bring the pleural cavity in contact with the air produce irritation and delay cicatrization by apposition of the two pleural folds. The resistance of the pleura to the infection becomes diminished by contact with air. The authors describe a medical treatment of empyema. The aspiration of pus is followed by a lavage of the pleura with luke-warm physiological saline solution in large amounts (one to three quarts). This is repeated at intervals of forty-eight hours. After X-ray studies show reduction of the empyema the lavages are done at longer intervals. Small transfusions of whole blood from 100 to 150 cc. are given to maintain the resistance of the patient. The authors have treated a number of cases this way. In their latest report they have added 20,000 to 40,000 units of penicillin to the saline solution; 5,000 to 15,000 units of penicillin were given intermuscularly every four hours for one to two days. In the 2 cases so treated complete cure was obtained in forty-five days. In a third case 30,000 to 35,000 units of penicillin were injected intrapleurally without pleural lavage every twenty-four hours and after four days every forty-eight hours. The pus became sterile, but the fever persisted. Seven days after the last intrapleural administration of penicillin the pus was evacuated by pleural puncture and after lavage with saline 80,000 units of penicillin were instilled intrapleurally. Complete cure was obtained in twenty-six days. In all 3 cases the pus was found to be sterile twenty-four hours after application of the penicillin. The closed lavage of the pleural cavity helps to eliminate the toxic products of the suppuration and prevents mixed infection so often occurring in pyopneumothorax. Penicillin should be used intrapleurally; 50,000 units should be injected intrapleurally every twenty-four hours for four days and every forty-eight hours thereafter until afrebility is obtained. In the presence of other inflammatory processes additional intramuscular administration of 20,000 units of penicillin every four hours may be necessary.—*Tratamcinto medico del empiema pleural metaneumonico, R. Gondar, F. Saffie & J. Bonell, Rev. méd. de Chile, January, 1945, 73: 80.—(W. Swienty)*

Local Penicillin in Lung Abscess.—A chronic putrid lung abscess had been treated with intramuscular penicillin without marked benefit. The patient continued to go downhill and hemorrhages continued. The abscess was located in the apical portion of the right lower lobe. The organisms involved were predominantly *Streptococcus viridans*. Also present were *N. catarrhalis*, fusiform bacilli, pneumococci and two other strains of streptococci. Because of the desperate condition of the patient, local administration of penicillin was decided upon. Thick pus was aspirated from the chest at a point about 2 inches from the midline posteriorly, in the seventh posterior intercostal space. At a depth of 8 cm. thick pus was encountered and 20,000 units of penicillin in 5 cc. of saline was instilled. On following days different spots were chosen for the injection after preliminary aspiration of pus each time. The condition improved remarkably. After the first injection the temperature became normal. However, although the symptoms were controlled by this treatment the abscess as seen on X-ray film did not close. Surgery was decided upon, and after resection of two ribs the abscess cavity was located and a drain placed. The interlobar fissure was tremendously thickened and contained pus. The patient died shortly after the operation.

Autopsy shows acute peritonitis resulting from an apparently rather silent gastric ulcer. It is felt that this patient was benefited by the local application of penicillin, and benefit might have been more apparent had he been treated in this fashion more promptly.—*Local Instillation of Penicillin in Lung Abscess, D. Pickering & R. Greenville-Mathers, Lancet, April 28, 1945, 248: 580.*—(*H. Marcus*)

Surgical Treatment of Lung Abscess.—Eighty-five cases of lung abscess were treated surgically with a mortality of 16.5 per cent. External drainage was performed in 77 cases: in 3 cases lobectomy was done (2 deaths); 3 apical thoracoplasties were performed (2 good and 1 doubtful result); in one case Monaldi's aspiration with subsequent apical thoracoplasty was done. In 3 cases the abscess drained spontaneously through the bronchus after institution of a pleural tamponade, preliminary to further surgery. In 15 of these cases the condition had persisted for more than one year and in this group there were 13 deaths. In the group of cases that were operated on soon after the onset of the condition, there were 2 deaths (one due to an air embolus and one due to a secondary pyopneumothorax). In 3 cases a bronchocutaneous fistula persisted after external drainage. No fistulae occurred in cases operated on less than three months after onset of the condition. No case of bronchiectasis was observed in lung abscesses of less than three months' standing. Early surgery, therefore, not only gives a smaller death rate but prevents occurrence of secondary complications. Recurrence of a lung abscess occurred in 2 cases, four and eighteen months after institution of external drainage.—*Les résultats du traitement chirurgicale de l'abscès du poumon: A propos de 85 observations, P. Sauty & M. Bérard, Presse méd., August, 1944, No. 15, 225.*—(*G. Simmons*)

Penicillin Treatment of Pulmonary Suppuration.—Local and systemic treatment with penicillin was tried in hemothorax, pyogenic empyema, mixed infection tuberculous empyema, extrapleural suppuration and pulmonary suppuration. Intrapleural instillation of penicillin into uninfected hemothorax cases apparently prevented infection. However, deposition of fibrin goes on regardless of treatment and, when this becomes extensive, rib resection and evacuation of fibrin and clot become necessary. Postoperatively penicillin appeared to be of value in preventing infection. Pyogenic empyema is almost never cured by aspiration of pus and instillation of penicillin. Although the pus may become sterile, a rigid pleural space results, and the lung does not reëxpand. Thoracotomy and drainage became necessary. Penicillin again is valuable following operation when instilled into the pleural cavity. Administration of penicillin into the pleural cavity may be of value before an empyema becomes thick, and if the underlying lung process is still active. This is especially true of hemolytic streptococcus infections. In secondarily infected tuberculous empyemata penicillin treatment has been of distinct value. Although drainage may eventually become necessary, all patients were benefited with return of temperature to normal and disappearance of the secondary invaders from the pleural exudate. The single dose is 20,000 to 50,000 units given intrapleurally at intervals from one to four days. The total dose is up to 400,000 units. Penicillin is useless if the only infecting organism is penicillin resistant, but if several organisms are present, one penicillin sensitive and one resistant, distinct improvement has resulted, with eventual disappearance of both organisms. Extrapleural infections following upon surgery of the thorax are successfully treated if the organism is sensitive. The cases of intraplulmonary suppuration fall into several groups. Infection with nonhemolytic microaerophilic streptococci is fairly common. The organism is penicillin sensitive, but, although the infection of the lung can be treated successfully with intramuscular administration of 60,000 to 120,000 units of penicillin for about two weeks, complications have been

frequent. Empyema could not be aborted, and cerebral abscesses have occurred in 3 out of 7 such cases. Pulmonary suppuration due to mixed anaerobic infection has not been treated successfully in spite of the fact that the organisms were penicillin sensitive. Surgical drainage became necessary in 5 out of 6 cases treated with penicillin. Two cases of actinomycosis were also treated. Good results were obtained in one case, but treatment was protracted and the dosage high. This patient received one course of 1,800,000 units over a course of six weeks. Three weeks later he had a recurrence and another course of penicillin was given. The second course lasted twenty-eight days, and 5,600,000 units were given. The patient remained well for a four-month period.—*Pleural and Pulmonary Suppuration Treated with Penicillin, J. E. H. Roberts, O. S. Tubbs & M. Bates, Lancet, January 13, 1945, 248: 39.*—(*H. Marcus*)

Absorption of Aerosol Penicillin.—The absorption of penicillin by the lungs was studied experimentally. Solutions of penicillin containing 10,000 units of penicillin per cc. were dispersed in a room of 3,000 cubic feet by means of an electric generator. Twenty cc. of a solution of sodium penicillin in water could thus be dispersed in an hour. An extremely fine mist was produced. Blood agar cultures which had previously been inoculated with 500 colonies per plate of staphylococcus aureus showed complete inhibition of growth if the plate was exposed in the room at a distance of 25 feet from the generator for fifteen minutes at the start of the experiment and for five minutes towards the close of the hour. Considerable quantities of penicillin were noted in the blood and in the urines of volunteers who were exposed to the aerosol penicillin. After thirty minutes' exposure in the room, one part of urine was sufficient to inhibit the growth of staphylococcus aureus when added to 19 parts of a broth culture. The possible practical applications of these experiments are obvious. It has been demonstrated that aqueous sodium penicillin remains active for a considerable time when dispersed as an aerosol. The dispersion of penicillin in entire hospital wards, operating or dressing rooms thus becomes a practical procedure. The administration of penicillin to patients who object to both intramuscular injections or to the use of face masks, or the administration to extremely young patients, can be satisfactorily solved in this manner.—*Absorption of Aerosol Penicillin via the Lungs, F. A. Knott & W. H. Clark, Lancet, April 14, 1945, 248: 468.*—(*H. Marcus*)

Penicillin by Inhalation.—Experiments were conducted in 5 normal subjects to determine the feasibility of administering penicillin via the respiratory tract by means of nebulization. A Collison nebulizer was used and oxygen passed through it at the rate of 8 to 10 liters per minute. The concentration of penicillin was 80,000 units per cc. The mist was delivered by means of the nose piece of the standard BLB mask. The patient inhaled through this and was instructed to exhale through the mouth. At least 40,000 units can be absorbed during a half-hour period, and effective blood concentrations can be obtained. Maximal excretion followed during the half hour after the conclusion of the experiment. The waste of material is high, amounting to from 60 to 75 per cent of the material. It is possible, however, that weaker solutions, such as 5,000 units per cc., might be employed to equally good advantage, thus making the procedure practicable for treatment of infections of the lower respiratory tract. Aqueous calcium penicillin was used because sodium penicillin solution was found too irritating.—*Penicillin by Inhalation, N. Mutch & R. E. Rewell, Lancet, May 26, 1945, 248: 650.*—(*H. Marcus*)

Bronchiectasis following Atypical Pneumonia.—Primary atypical pneumonia, etiology undetermined, is usually a mild to a moderately severe illness affecting young adults. The duration of the disease is from five to fourteen days; it is uninfluenced by

chemotherapy. The literature of the clinical, roentgenological and pathological findings of atypical pneumonia is reviewed. Two factors responsible for the development of bronchiectasis may be present in atypical pneumonia, bronchial infection and bronchial obstruction. Twenty patients with bronchiectasis following attacks of atypical pneumonia during the winter of 1942–1943 were seen. In all of them, roentgenograms taken at the time of induction into the Army had been normal. These patients had had no symptoms prior to the pneumonia. There was no spontaneous healing of the atypical pneumonia; productive cough, râles and roentgen signs of unresolved pneumonia persisted. Bronchographic examination after several months revealed bronchiectasis. Bronchography was repeated over a period of two to six months. In 3 patients the bronchiectasis disappeared. Ten of the 17 patients had lobectomies with complete relief of symptoms, without operative mortality. Pathological examination of the resected lobes confirmed the diagnosis. Seven representative case histories are given.—*Bronchiectasis ollowing Atypical Pneumonia, E. B. Kay, Arch. Int. Med., February, 1945, 75: 89.—(G. C. Leiner)*

Bronchiectasis.—The following theories regarding etiology are listed: (*1*) preëxistent recurring bronchial infection, (*2*) chronic lobar or lobular pneumonia, (*3*) pertussis with pneumonia, (*4*) acute or chronic lung abscess, (*5*) bronchial obstruction due to carcinoma, (*6*) foreign body, (*7*) inflammatory cicatrix caused by specific infection, as tuberculosis, or caused by various nonspecific infections, and (*8*), to a lesser extent, chronic empyema or lesions causing gradual bronchial compression with retention of secretions and subsequent infection. The authors do not believe that sinus disease is frequently concomitant. Pathologically bronchiectasis is characterized by a degeneration of the bronchial wall with infection, the inflammation and necrosis of the tissue extending beyond the bronchial walls and, in advanced cases, producing bronchopulmonary suppuration. The diagnosis is based early on the presence of slight cough with scanty or moderate amounts of nonfoul sputum and, occasionally, hemorrhage. At this period the patient's general condition is good. Physical signs may be absent or, if present, may consist of diminished resonance and râles. Later, however, cough becomes severe, sputum is abundant and foul, clubbing is frequent, hemorrhage is by no means unusual, and, when drainage is impaired, there is severe sepsis. The complications are: (*1*) hemorrhage, which is quite common (Hedblom is cited as authority for the statement that hemorrhage occurs probably more often in bronchiectasis than in tuberculosis); (*2*) bronchopneumonia (the patient is usually not quite so toxic as in primary pneumonia and recovery is often more rapid); (*3*) atelectasis, which is due to obstruction by inspissated secretion or by the cicatrix of chronic inflammation (when atelectasis is permanent, there is produced the "shrunken lobe" of Jones and Cournand); (*4*) empyema. The authors point out that diagnoses on plain films are not consistent, but may be suspected from prominent bronchial markings, from rounded areas of increased radiance, the so-called "honeycombs," from lobar or lobular atelectasis, and from areas of mottled densities. The means of choice for diagnosis of bronchiectasis are bronchography and bronchoscopy with suction to remove secretions in those cases where visualization is not good due to inspissated secretions or cicatricial stenosis. Tuberculosis, foreign body, bronchogenic carcinoma and lung abscess must be differentiated from bronchiectasis. The authors present the following pathological classification: (*1*) ulcerative, the type in which hemorrhage is frequent; (*2*) stenotic, which favors the development of atelectasis and the progression of infection; (*3*) fibrotic, in which abundant peribronchial fibrosis exerts a traction mechanism; and (*4*) the "dry hemorrhagic" type not characterized by either cough or sputum but rather by recurrent hemorrhage. This latter type may be on a congenital basis, and

these cases often give a negative history. Both physical examination and X-ray may be negative. However, the bronchogram clinches the diagnosis. Anatomically the cylindrical type is most common and is most often found at the bases. The saccular is less common and occurs more often in the upper lobes. Occasionally there is a fusiform type. All cases reported in this study were confirmed by bronchogram except where lipiodol instillation presented difficulty or where atelectasis was evident, or neoplasm was suspected. Sixty-two cases were presented. There was a considerable incidence of antecedent respiratory disease. Chronicity was an important factor. Râles were present in 93 per cent. There was a history of hemoptysis in one-third. Clubbing and foul sputum were relatively infrequent. Fifty per cent of the lesions were located in the left lower lobe, 31 per cent in the right lower lobe, 12 per cent in the right middle lobe, and 16 per cent in both lower lobes. None occurred alone in either upper lobe. The incidence of bronchiectasis in the Army does not exceed that in civilians. It was present before induction. Mobilization regulations stipulate bronchiectasis as disqualifying. The C.D.D. board is authorized to recommend discharge on a Certificate of Disability, after which, if the individual is in need of hospital care, he is eligible for admission to a Veterans' Hospital. A group of case reports is presented. Of 1,753 cases observed at the Station Hospital since September, 1940, and separated from the service for various causes, 32 cases, or 2 per cent, were discharged because of bronchiectasis.—*The Diagnosis of Bronchiectasis: Clinical and Roentgenological Observations, M. H. Joress & S. A. Robins, Dis. of Chest, November–December, 1944, 10: 489.—(K. R. Boucot)*

Atelectasis and Bronchiectasis.—The decreased endothoracic pressure consecutive to bronchial obstruction and atelectasis is considered by many as the chief mechanism in the pathogenesis of bronchiectasis. In face of this tendency, it is useful to reconsider the question of the relationship between atelectasis and bronchiectasis. Experimental studies, clinical and roentgenological evidences have proved that with decreased endoalveolar pressure there is a tendency in the obstructed bronchus also to collapse and that this tendency cannot be counteracted by decrease of endothoracic pressure. Bronchial obstruction causes the bronchus to dilate only when it is incomplete; in this case there is no atelectasis, but obstructive emphysema. Infection is the most important single factor in the genesis of bronchiectasis. The inflammatory process causes deep changes in the various structures of the bronchial wall. The secondary mechanical factors act on the weakened bronchus in establishing an irreversible bronchial dilatation. The bronchial occlusion facilitates the development and persistence of infection, and the incomplete occlusion with a valve-mechanism in the presence of infection also favors the dilatation of the bronchi in the blocked segment. A superimposed infection can also cause a latent congenital or acquired bronchiectasis to become clinically significant. The rapidity with which bronchiectasis develops depends upon the association of the different factors, among which pleuropulmonary fibrosis should also be mentioned. The rôle of infection is emphasized by the observation that not all cases of atelectasis are followed by bronchiectasis. The higher incidence of bronchiectasis in children can be explained by the narrower bronchi, by the less powerful expectoration and by the more delicate anatomical structures in children. The sequence of events in the case of bronchiectasis associated with tuberculosis brings further evidence in favor of the above described pathogenetic view. Experimental studies also support this opinion. The prevention and treatment of bronchiectasis, therefore, consists essentially in the treatment of all infections of the respiratory tract (chemotherapy) and in all measures that prevent retention of secretions and bronchial obstruction, such as symptomatic treatment, postural drainage, removal of foreign bodies, bronchoscopic aspiration, appropriate

pre- and postoperative care, etc.—*Atelectasia pulmonar y dilatación bronquial-relaciones recíprocas, R. F. Vaccarezza & J. M. Leston, An. Cáted. de pat. y clin. tuberc., 1943, 5: 5.*—*(L. Molnar)*

Loeffler's Syndrome.—Two cases of transient pulmonary infiltrate with moderate eosinophilia are presented. The rapid disappearance of the infiltrations (two weeks) with complete *restitutio ad integrum* and the blood picture (4 per cent eosinophils, 26 per cent lymphocytes) excluded the possibility of a specific pulmonary involvement. No allergenic factors, such as the presence of ascaris in the feces, could be demonstrated. One of the patients, however, had tuberculous peritonitis and the other had been previously exposed to tuberculosis. It is believed that in both cases the transient infiltrate was the expression of an allergy against "tubercle toxins."—*Contributo allo studio dei cosidetti "infiltrati polmonari fugaci," V. Gramazio, Ann. Ist. Carlo Forlanini, 1942, 6: 237.*—*(G. Simmons)*

Therapy of Bronchial Asthma.—An attack of bronchial asthma can be produced experimentally in a guinea pig by exposing the animal to the inhalation of a finely dispersed solution of histamine. Such a "histamine-asthma attack" may well serve for the study of the prophylactic or therapeutic value of different substances. Dioxyephedrine is particularly efficacious against histamine asthma and the effect of this substance can be enhanced further by addition of diphenylpiperidicopropane.—*Experimentelles zur Asthmatherapie, O. Schaumann, München. med. Wchnschr., 1942, 11: 742.*—*(G. Simmons)*

Pulmonary Acariasis.—During a two-year period the authors discovered that bronchial asthma was responsible for 48 per cent of respiratory cases and 21 per cent of all cases invalided out of the Army from their medical division. In general, the observations on these cases showed (*1*) the presence of eosinophilia, in some cases of a very high degree; (*2*) essentially negative past or family history of asthma or other allergic manifestations; (*3*) exclusion of alimentary parasitism by the usual pathological tests and (*4*) poor response to the usual medical treatment of asthma. Because of previous reports of success, a search was made for mites in the sputum—and in 11 of 21 cases whose sputum was examined by a special technique the mites were found. They were mites of either *tyroglyphus* or *tarsonemus*. The radiological findings in these cases were typically those of fine, diffuse mottling, giving a ground glass appearance. Reëxamination of the lungs after arsenical treatment showed a clear parenchyma. The treatment consisted in arsenicals of the pentavalent variety and resulted in remarkable success—with a marked reduction in the eosinophilia as well as distinct clinical improvement. The disability was acquired after the inhalation of mite-laden air. The majority of the patients had been exposed to dust emanating from rice, cereals, flour, sugar, etc. A few had worked in linen and leather goods depots. The frequent existence of tyroglyphid and tarsonemid mites in stores and stored products has been recognized. In conclusion the authors state that the possibility that pulmonary acariasis may be responsible for other respiratory disorders besides asthma should not be ignored and that the treatment of all such cases, whether asthmatic or otherwise, by the administration of pentavalent arsenicals is worthy of consideration.—*Pulmonary Acariasis: A Possible Cause of Asthma, E. Soysa & M.D.S. Jayawardena, Brit. M. J., January 6, 1945, 1: 1.*—*(D. H. Cohen)*

Parasitic Diseases of Lung.—In 2 people who had had long contact with animals (dogs and foxes) multiple round shadows of the size of a small nut and containing an irregularly limited denser nucleus were seen, localized near the pleura. Clinically there was acute onset of dyspnea and acute bronchitis. Similar pictures had been described previously and it was believed that they were due to pulmonary localization of the ova of *Taenia*

solium. The author believes, however, that his 2 cases, as well as some of those described as cysticercosis, may have been due to the pulmonary localization of *Pentastomum denticulatum*, an arachnoid, which often has man as an intermediate host. The larvae of this parasite may reach the lung via the blood or the lymphatic system and die there (or in the liver), whereas ova of *Taenia solium* are more frequently found in the brains and in the muscles.—*Zur Differentialdiagnose der parasitären Lungenerkrankungen. Cysticercose-Pentastomiasis, F. Weiser, Beitr. z. Klin. d. Tuberk., 1942, 98: 259.*—(*G. Simmons*)

Ornithosis.—Ornithosis is a virus disease. Infections in human beings may occur by direct contact with infected birds, by inhalation of infected droppings or by contact with an infected person. The incubation period is probably eight to fourteen days. The onset of the disease is usually abrupt, with high fever, headache, malaise, nonproductive cough. The physical findings are fluctuating fever with relative bradycardia; rose spots have been observed. The pulmonary findings may vary from normal to frank consolidation, often migrating from one lobe to another. The white blood cell count is elevated at the onset but later on leucopenia may develop. The pulmonary roentgenological findings may vary from increased hilar markings to migratory, patchy infiltrations or pneumonic consolidation. The duration of the febrile course varies from one to five weeks. The very severe form is accompanied by cyanosis and toxic cerebral symptoms. It ends fatally in 35 to 45 per cent. The most important diagnostic procedure is the isolation of the virus from the sputum by inoculation into mice. Until the fourth to tenth day the virus can be isolated from the blood. If no sputum is available the complement fixation test is the most reliable diagnostic procedure provided no infection with the virus of lymphogranuloma venereum is present since these viruses are antigenically related. There is no specific treatment for ornithosis. Experimental evidence points to penicillin as a valuable aid in its therapy while sulfonamides are ineffective. During the past two years 6 sporadic cases of atypical pneumonia were observed in Philadelphia in which a diagnosis of ornithosis could be made by means of the complement fixation test. A history of direct contact was obtained in 2 cases, in the remaining 4 cases daily exposure to pigeons had occurred. The sera of 14 pigeons captured in Philadelphia were tested for the complement fixation titre to ornithosis. The test was positive in diagnostic dilutions in 6 pigeons. Infection of pigeons with ornithosis averaging 40 to 50 per cent is probably of universal occurrence. While cold agglutinins are frequently found in atypical pneumonia they could not be demonstrated in cases of ornithosis.—*Ornithosis as a Cause of Sporadic Atypical Pneumonia, D. C. Levinson, J. Gibbs & J. T. Beardwood, Jr., J. A. M. A., December 23, 1944, 126: 1079.*—(*H. Abeles*)

Treatment of Ornithosis.—A 43 year old man who had a loft of homing pigeons took ill with fever, generalized aching and abdominal discomfort. Physical examination revealed slight impairment of mental coördination, photophobia, atypical consolidation of the left lower lobe, splenomegaly, gaseous, abdominal distention and relative bradycardia. The white blood cell count was 9,200. X-ray examination of the chest revealed a central, pneumonic infiltration in the left lower lung. A specimen of the patient's serum obtained on the fifth day of his illness fixed psittacosis antigen in a dilution of 1:256. On the fifth day of his illness the patient was started on 100,000 units of penicillin daily. After the fifth day of treatment the temperature was normal. One month after the onset of his illness the patient returned to work. The virus of ornithosis was recovered from the spleen of one of the pigeons of the patient's loft.—*Human Ornithosis Treated with Penicillin, F. E. Turgasen, J. A. M. A., December 30, 1944, 126: 1150.*—(*H. Abeles*)

Lymphogranuloma Venereum Virus Infection of Respiratory Tract.—After reviewing briefly the literature on experimental and human respiratory infection with this virus, the author refers to his experiences with the entity. In acute cases, whether by buccal or genital invasion of the virus, he has found in some cases the coexistence of tracheobronchial signs, and in chronic cases, such as vulvar erosion, rectal stenosis, peno-scrotal elephantiasis, signs of intense pulmonary fibrosis and involvement of the mediastinal lymph nodes, etc., without its being possible to relate it to tuberculosis. A case history is given of a 46 year old mechanic who for some years had had an ulceration of the gum, slowly growing and resistant to all treatment. A positive Frei test was obtained and biopsy revealed lymphogranuloma virus in large quantities. The patient died of a hemorrhage from rupture of a branch of the internal maxillary artery, caused by extensive ulceration. Necropsy showed intense fibrosis and nodulation of the right lung and marked fibrosis in the alveolar septa, formation of fibrous cortical and subcortical nodules and fibrosis and thrombosis of the vascular system in the left lung. The gum ulcer and the cervical and mediastinal lymph nodes showed intense fibrosis. Great quantities of virus were found in all tissues studied. No evidence of cancer or tuberculosis was found. The author believes pulmonary infection by lymphogranuloma virus can be by direct mucosal extension from a lesion high in the respiratory tract, by the lymphatics or by the circulatory system in which latter case the early symptoms are of the catarrhal type.—*Infeccion del aparato respiratorio por el virus linfogranuloma venereo (L. V.), W. E. Coutts, Rev. chilena de hig. y med. prev., January, 1944, 6: 163.*—*(J. S. Peterson)*

Acute Interstitial Fibrosis of Lungs.—This report adds another case of this rare pulmonary disease to the 4 already reported by Hamman and Rich. A 47 year old Italian-born male was admitted to the Peter Bent Brigham Hospital suffering from severe dyspnea and a dry cough. Physical examination revealed only a few transient râles in the left axilla, but the heart was found to be slightly enlarged to the left and the pulmonic second sound was louder than the aortic. The fingertips were clubbed. The patient had been in good health until four months before admission, when the dyspnea was first noted. X-ray films of the chest showed extensive fine mottling of both lungs most marked in the upper lobes, findings suggestive of miliary tuberculosis. The tuberculin test (first strength), however, was negative and no tubercle bacilli were found in the sputum. A few days after admission fever developed and the respiration became rapid with marked cyanosis. Both legs became mottled and cool below the mid-calf. Many more petechia appeared over the abdomen and anterior chest. Although oxygen administration afforded temporary relief from the air hunger the patient died in respiratory failure eight days after admission. Two days before death a pleural friction rub was heard in the right axilla. At autopsy both pleural cavities were found to be obliterated by moderately dense fibrous adhesions. On sectioning, the lung surfaces presented the mosaic appearance of diffuse fibrosis with interspersed areas of emphysema and pneumonic consolidation. Microscopically there was striking and extensive interstitial fibrosis throughout both lungs. The alveolar walls were found to be greatly thickened by recently formed connective tissue and capillaries. The aveoli were lined by very prominent epithelium and some contained cell debris and phagocytes. The bronchioles were relatively free from exudate. There was no bronchiectasis. Many of the small pulmonary vessels showed obliterative fibrosis. There was no evidence of tuberculosis. Except for some hypertrophy of the wall of the right ventricle the heart was essentially normal. The aorta contained extensive friable antemortem thrombus overlying and entering several of the intercostal arteries. The right iliac artery was occluded by adherent thrombus; a free thrombus partly

occluded the left iliac artery. Infarcts were found in the kidneys and pancreas. The resemblance of the present case to those described by Hamman and Rich is striking. The proliferation and prominence of the lining alveolar epithelial cells seem identical with the changes mentioned by the above authors. Apart from focal areas of terminal bronchopneumonia there were no stainable bacteria in the pulmonary tissue and there was no residuum of the type of inflammation usually produced by pyogenic bacteria. These negative findings also characterized the 4 previously reported cases. The etiology of the underlying pulmonary disease remains obscure. (Illustrated.)—*Report of a Case of Acute Interstitial Fibrosis of the Lungs, H. Eder, C. Van Zandt Hawn & G. Thorn, Bull. Johns Hopkins Hosp., April, 1945, 76: 163.—(J. S. Woolley)*

Coccidioidin Tests and Pulmonary Findings.—Only since 1937 has it been recognized that *C. immitis* can cause a wide-spread, benign, pulmonary infection as well as the more severe coccidioidal granuloma with its 50 per cent mortality. The demonstration that the minor respiratory illnesses often associated with erythema nodosum and commonly called "Valley Fever," from its prevalence in the San Joaquin Valley of California, were due to *C. immitis* has stimulated wide-spread epidemiological study. A variety of pulmonary manifestations have been reported in early coccidioidomycosis, namely, bronchial pneumonia, subacute and chronic cavitation resembling tuberculosis and calcified pulmonary lesions. The relationship of healed and calcified pulmonary lesions to positive coccidioidin skin tests forms the basis of this report. Skin testing for sensitivity to coccidioidin as a diagnostic aid or in epidemiological surveys has demonstrated a surprisingly high incidence of reactors depending largely on the locality of the study. In fact, the testing of the school children of the Pima Indian Reservation of Arizona yielded such a high incidence of positive cutaneous reactions (90 per cent) that the test material was first thought to be nonspecific. However, the same antigen, when used in testing Philadelphia children, gave no positive reactions. The clinical material for the present study came from Arizona, New Mexico and the southern part of California. For routine skin tests, 0.1 ml. of a 1:100 dilution of coccidioidin (Smith) was used and the tests were read, together with controls, at twenty-four and forty-eight hours. An area of erythema of 1 cm. or more was accepted as a positive reaction. Purified protein derivative was used for the tuberculin skin tests. The lungs of autopsied cases were removed intact for roentgenological studies. In this way calcified and fibrotic areas were localized and then excised from the lungs and peribronchial lymph nodes. One-half of the excised material was treated and injected into the testicles of guinea pigs and the remainder was decalcified and sectioned. Results: skin tests with coccidioidin were performed on 1,165 patients. Of these, 302, or 25.9 per cent, were positive reactors. According to geographical distribution the incidence of infection was, in part, as follows: The San Joaquin Valley, 62.8 per cent; Arizona, 28 per cent; and Texas, 35.7 per cent. These figures agree rather well with the known distribution of endemic areas of coccidioidomycosis. Approximately 400 of these cases were tested with tuberculin. Comparative studies showed no cross-antigenic relationship between tuberculin and coccidioidin. Skin antigens of other fungi (torula, aspergillus, blastomyces and sporotrichum) prepared in a manner similar to that for coccidioidin produced no skin reactions in patients sensitive to coccidioidin. Thirty-six patients upon whom skin tests had been done were examined by autopsy. Twenty-five had not reacted to coccidioidin. Four of these showed no calcified lesions. The remainder exhibited calcified areas of different sizes in various parts of the lung mostly in moderate numbers. Most of these lesions were interpreted as residual evidence of healed primary tuberculous foci. The lungs of 3, however, suggested a healed miliary type of tuberculosis.

Tubercle bacilli were not found in material from these cases. Two cases dying of advanced coccidioidal granuloma were also negative to coccidioidin. This is not an infrequent finding. Eleven cases with a positive coccidioidin skin reaction dying of intercurrent disease were seen at autopsy. All showed some areas of calcification (or encapsulated necrosis). In 9, endospores or spherules were found but only one positive culture for *C. immitis* was obtained. None showed tubercle bacilli. No clear clinical histories suggestive of coccidioidomycosis infections had been obtained in these positive reactors. The calcified lesions were indistinguishable grossly from similar lesions of tuberculosis except that apical scars were not a part of the healed or arrested pulmonary phases of coccidioides. The histological pattern was essentially that of tuberculosis except for the presence of the spherules. The centres were caseous and contained small calcified particles and faint outlines of necrotic lung tissue. Each lesion was surrounded by a dense, hyalinized, fibrotic capsule, external to which were collections of lymphocytes. The spherules, some containing endospores, were located in the capsules. In none of the animals injected with material from the healed lesions was a lesion of coccidioides or tuberculosis demonstrated. Undoubtedly most of the healed lesions were of tuberculous origin. This would indicate that in healed tuberculosis, as well as healed coccidioidomycosis, the organisms are dead. This is another point in which these two diseases resemble one another. (With 5 plates.)—*Healed or Arrested Pulmonary Coccidioidomycosis: Correlation of Coccidioidin Skin Tests with Autopsy Findings, E. M. Butt & A. M. Hoffman, Am. J. Path., May, 1945, 21: 485.*—(*J. S. Woolley*)

Pulmonary and Meningeal Torulosis.—Very few cases of infestation of the lung by yeast cells are published. The author presents one case. The first symptoms experienced by the patient, a woman of 45 years, were severe headache, nausea and projectile vomiting. She had marked papillary edema, moderate dyspnea and cough. On auscultation subcrepitant and sibilant râles were heard over the middle portion of the right lung. The cerebrospinal fluid revealed yeast-like fungi which were diagnosed as *Torula histolytica* (*Cryptococcus histolyticus*). In the culture the fungus grew in round cells with double membranes by budding only. The patient died in delirium. The autopsy showed abundant exudate in the subarachnoid spaces which was formed by peculiar polynuclear cells and macrophages. In the right lung there was an abscess containing thick pus. In its wall and also in the neighboring pulmonary tissue isolated round fungus cells with double membranes were found. The tissue reaction to these fungus cells was similar to that observed in the infectious granulomata. Primary pulmonary torulosis is rare, whereas the secondary form associated with cerebral infections is more frequent. This, the patient presented. Pulmonary torulosis may simulate an abscess of the lungs. The presence of yeast cells in the exudate and the absence of the diagnostic elements of tuberculosis or neoplasm can lead to the diagnosis. The value of the specific vaccine in the treatment has yet to be proved.—*Estudio clinico y anatomo-patologico de un caso de torulosis meningoencefalica y pulmonar, T. Castellano, Rev. Asoc. méd. argent., November 30, 1944, 58: 1051.*—(*W. Swienty*)

Nontuberculous Pulmonary Calcification.—In the central eastern half of the United States there is an area of high prevalence of calcified pulmonary lesions. Many of these cases are negative to tuberculin and to coccidioidin. Tuberculin, histoplasmin tests and chest roentgenograms were done in 3,105 student nurses in Minneapolis and St. Paul, Minnesota, Kansas City, Missouri, Kansas City, Kansas, Detroit, Michigan, and Philadelphia, Pennsylvania. The tuberculin tests were performed with Purified Protein Derivative, the histoplasmin tests with 0.1 cc. of a 1:1,000 dilution of a filtrate of broth culture of *Histo-*

plasma capsulatum. Seven hundred and eleven (22.9 per cent) showed a positive reaction, 61 (2.0 per cent) a doubtful reaction to histoplasmin. Two hundred and ninety-four had pulmonary calcifications. Of these, 21.4 per cent reacted to tuberculin. Of the remaining 231, 206 (70.1 per cent) had a positive or doubtful histoplasmin reaction. Only 25 (8.5 per cent) had a negative reaction to both tuberculin and histoplasmin. Among the nurses who reacted only to tuberculin, 10.4 per cent showed pulmonary calcifications; among those who reacted only to histoplasmin, 31.1 per cent showed calcifications; among those who reacted to both antigens, 36.1 per cent showed calcifications; among the 2,141 nurses who were negative to both antigens, only 25 (1.2 per cent) had pulmonary calcifications. The author draws the following conclusions: (*a*) Mild, probably subclinical infection with *Histoplasma capsulatum* (or an immunologically related organism) is widely prevalent in certain states and relatively infrequent in others. (*b*) In general, those states in which the frequency of reactions to histoplasmin is high are those in which pulmonary calcification is also high. (*c*) A very high proportion of the pulmonary calcifications observed in roentgenograms of tuberculin-negative persons is due, not to tuberculosis, but probably to histoplasmosis. —*Nontuberculous Pulmonary Calcification and Sensitivity to Histoplasmin*, *C. E. Palmer*, *Pub. Health Rep.*, *May 11, 1945*, *60: 513*.—(*G. C. Leiner*)

Echinococcus.—A case of echinococcus cyst of the heart is presented. The clinical diagnosis is based on characteristic roentgenoscopic and roentgenographic evidence of a calcified cyst in the heart wall along with electrocardiographic evidence of myocardial changes and a positive intracutaneous test with echinococcus antigen in the absence of other types of cestode infestation. (Authors' Summary)—*Echinococcus Cyst of the Heart*, *J. Zizmor & M. M. Szucs*, *Am. J. Roentgenol.*, *January, 1945*, *53: 15*.—(*P. Lowy*)

THE

AMERICAN REVIEW OF TUBERCULOSIS

ABSTRACTS

VOLUME LIII MARCH, 1946 ABST. No. 3

Inhalation of Cold Air.—Dogs were caused to breathe extremely cold air for periods ranging between twenty and one hundred and thirty-three minutes. The cold air was brought into the mouth of the animals through a vacuum-jacketed (Dewar) cannula. The temperature of the air was between −50 and −28°C. when it reached the larynx. When the air reached the bifurcation of the trachea it had been warmed to a temperature of above +18°C.; and when it left the lungs it was within 1 or 2 degrees of normal. The rectal temperature dropped in no animal. The only ill effects were hyperactivity of the mucous glands of the upper respiratory tract, coughing and hoarseness. One animal died of obstructive edema of the pharynx and larynx, caused by direct contact of the cold tip of the laryngeal cannula with the adjacent tissues. In the animals which were killed between four and twelve hours after the exposure there was some edema of the mucous membrane of the larynx, excessive secretion of mucus throughout larynx and trachea, small plate-like zones of atelectasis and subpleural zones of emphysema throughout both lungs. In the animals killed twenty-four hours after exposure there was damage of laryngeal and tracheal epithelium, small plugs of mucus mixed with desquamated epithelial cells in some of the smaller bronchi, plate-like atelectasis and emphysema. One animal killed forty hours after exposure showed less severe changes than the previous animals. The explanation of the rapid warming of inhaled cold air and of the occurrence of relatively mild and localized injury following the inhalation of cold air lies in the fact that dry air has an extremely low heat capacity and that the number of calories required to produce a great rise in the temperature of dry air can be provided by the heat derived from the cooling of a small amount of tissue by a few degrees. From these experiments it may be inferred (*a*) that it is unlikely that significant injury to the air passages of men would result from the breathing of air at any degree of coldness likely to be encountered in nonexperimental conditions so long as it was inhaled through the nose or between partially closed lips and (*b*) that, even though extremely cold air were inhaled rapidly through a widely opened mouth, it would be warmed to a point well above freezing by the time it reached the bronchi.—*Effects of Cold Air on the Air Passages and Lungs: An Experimental Investigation, A. R. Moritz & J. R. Weisiger, Arch. Int. Med., April, 1945, 75: 233.*—(*G. C. Leiner*)

Interstitial Emphysema and Subpleural Hematoma.—An 8 year old girl, who had been suffering from bronchial asthma for some years, had a severe asthmatic attack following which she complained of pain in her neck and chest; she developed dyspnea, swelling of the neck, a change of her voice. The diagnosis of subcutaneous, pulmonary and mediastinal emphysema was made. Five days later an X-ray examination of the chest was done which revealed a triangular paramediastinal shadow above the right diaphragm. The shadow had disappeared ten days later.

This shadow was believed to be produced by a subpleural hematoma. Two more cases of subcutaneous emphysema in bronchial asthma are described.—*Über interstitielles Emphysem und subpleurales Hämatom bei Asthma bronchiale. Ein Beitrag zur Differentialdiagnose bei paramediastinalem basalem "Dreieckschatten", L. Wallden, Upsala läkaref. förh., June 15, 1942, 47: 271.*—(*G. C. Leiner*)

Pulmonary Cysts. — Bronchopneumonectasis includes cysts of congenital (malformations) and acquired origin (deformations), classified as bronchiectasis, pneumonectasis and bronchiolopneumonectasis. The authors divide congenital cystic malformations into six groups: (*1*) pulmonary agenesis, (*2*) hypoplastic bronchiectasis (cystic anaplastic lung), (*3*) displastic bronchiectasis, (*4*) displastic bronchiolopneumonectasis (gaseous cysts), (*5*) hyperplastic bronchiolopneumonectasis (polycystic lung), and (*6*) displastic pneumonectasis (bullous emphysema). In general it is difficult and sometimes impossible to know whether the disease is congenital or acquired. This is likewise true of the clinical-radiological differentiation of some anatomical types. Bronchiectasis and bullous emphysema are predominantly of the acquired form and perhaps gaseous cysts also. Infection may be the causal factor or merely a complication revealing the presence of bronchopneumonectasis. Infection is of considerable importance in the development of obstruction and the subsequent apparition, insufflation and suppuration of the gaseous cysts. Cyst formations are frequently present as potential cavities with walls relaxed or in position and therefore invisible in the roentgenogram or tomogram. The insufflation of air or an accumulation of secretions distends the walls to form actual cavities. The rapid appearance and disappearance of a cavity as well as sudden modifications in its size are usual in bronchopneumonectasis. Complicating infection often renders apparent both clinically and roentgenographically a previously silent bronchopneumonectasis. The disappearance of a cystic shadow frequently occurs during the resolution of an intercurrent infection. The narrow communications between gaseous cysts or emphysematous bullae and the bronchial airway explain the frequent development of obstructive mechanisms whenever an inflammatory process happens to alter the physical state of the mucous secretions. The prevention of intracystic infection is based on the treatment of infection and bronchial obstruction. Sulfonamides and bronchial drainage are the two chief recourses. The authors report in detail 10 cases, in 2 of which pulmonary tuberculosis was a complication.—*El factor infección en las formaciones quísticas bronchopulmonares, R. Vaccarezza & J. Peroncini, An. Cáted. de pat. y clin. tuberc., December, 1943, 5: 199.*—(*R. Kegel*)

Concussion of Lung.—The frequent occurrence of gross pathological changes in the lungs of soldiers dying of wounds other than thoracic has stimulated this inquiry into the so-called "blast" lung. In a consecutive series of 87 autopsies, 30 instances of "blast" lung were found. All deaths were in soldiers who had serious head or abdominal wounds, and a few cases had severe burns. Although the method of wounding was unknown in 7 cases, it was felt that their lesions were identical with those who were known to have been exposed to blast. None of the cases had external evidence of damage to the chest, and none presented pulmonary hemorrhages. Some of the comatose cases did show fine râles at the lung bases, but in many cases it was felt that the obvious injuries should not have killed the patient. X-ray studies consistently showed less abnormality than was seen at autopsy. The picture was that of a scattered bronchopneumonia. It is difficult to diagnose the condition clinically, but it may be suspected in any patient who shows typical X-ray lesions of a patchy bronchopneumonia without physical signs of such, and whose other wounds are of such a nature that his condition should be better than it is. All variations in extent of the lesions were seen. When the involvement was mild, the lesions

were confined to the lower lateral portions of the lung. In the severe cases several or all lobes were involved. Grossly the hemorrhages vary from pinpoint to large confluent areas. Subpleural hemorrhage was seen ten times. Microscopically intraälveolar hemorrhages and congestion of the capillaries stood out. Bronchopneumonia was superimposed four times. Other organs showed similar hemorrhages in 10 cases.—*Pulmonary Concussion ("Blast") in Non Thoracic Battle Wounds, O. Savage, Lancet, April 7, 1945, 248: 424.*—*(H. Marcus)*

Air Embolism.—Pulmonary emboli may arise in the pulmonary veins in connection with practically every form of injury to these vessels. This type of embolism occurs relatively frequently in connection with artificial pneumothorax either through air being injected directly into a vein or by air in the pneumothorax cavity pouring into an injured vein. Since negative pressure often prevails in the pulmonary veins, air can be sucked into them, for example, on injury to a vein on the surface of the lung in pleural empyema or on puncture of or incision in the pulmonary parenchyma. On the basis of experiments on rabbits it was found that the average pressure in the left ventricle during inspiration was lower than the atmospheric pressure, regardless of the position of the animal. The experiments also indicated that the pressure was lower in the parts of the pulmonary veins above the level of the heart and that therefore air embolism was more likely to arise if the lesion was situated high up in relation to the heart. Judging by experimental and clinical experience, the site of the air emboli in the systemic circulation is highly dependent on the position of the body when the embolism develops. The dangerous symptoms are caused by emboli in the coronary circulation of the heart and in the cerebral vessels. In experiments on cadaver specimens, the risk of embolism in these vessels was found to be least in the supine position with the head elevated about 30 degrees. In this position, nearly all the air followed the blood-stream through the aorta and only very small amounts of air passed to the coronary vessels and the carotids. The air does not pass through the ordinary capillaries in the systemic circulation, but only through relatively wide arteriovenous anastomoses. Most of the air is absorbed from the precapillary vessels and thus does not reach over to the venous part of the circulation. This absorption occurs within an hour or so. Due to conglutination of corpuscles, the interruption of the circulation may continue even after the air has been absorbed. The symptom picture is generally dominated either by cardiac disorder or by signs of cerebral irritation or dysfunction. Quickly changing anemic or cyanotic patches on the skin and sharply outlined anemic areas on the tongue are sometimes of great help in the diagnosis. Air can be demonstrated by ophthalmoscopy soon after embolism has developed. Death occurs soon after the attack, a few hours later, or in occasional cases a day or so later. The patients who recover generally show no permanent ill effects. In order to reduce the risk of air embolism in irrigation of an empyemic cavity, provision must be made for the free escape of the air and water beside the tube or syringe used for irrigation. The patient should lie so that the cavity being irrigated is below the level of the heart. Punctures in the pulmonary parenchyma should also be made below the level of the heart. If blood is secured in the syringe on pneumonocentesis, it is dangerous to extract the needle before the patient has been placed so as to bring the site of the lesion below the heart. The use of a thermocautery instead of a knife to make the incision reduces the risk of air embolism. The thermocautery should be faintly glowing. Positive pressure respiration prevents air embolism from outside air, but does not prevent it from developing as a result of a bronchovenous communication produced, for example, by puncture through the pulmonary parenchyma. The treatment of air embolism should first be directed at preventing the formation of new emboli.

Artificial respiration can then be given, if indicated. Oxygen respiration and heart tonics probably have a favorable effect by facilitating the absorption of the air emboli. It is uncertain whether heart or vascular tonics or vessel-dilating preparations can hasten the passage of the air through the narrow vessels of the peripheral circulation. Nineteen cases of air embolism or suspected air embolism are described. All of them occurred in hospitals in Sweden during the years 1925 to 1938 in connection with the treatment of pleural empyema, with puncture of the lung for pulmonary abscess and with lobectomy or pneumonectomy. The rate of fatal air embolism in the treatment of pleural empyema in this material was at least 0.1 per cent and probably higher. The corresponding figure in puncture of the lung for pulmonary abscess was about 3 per cent. (Author's Summary.)—*Gas Embalism Originating in the Pulmonry Veins, V. Bahr, Upsala läkaref. förh., January 15, 1944, 49: 259.*—(*G. C. Leiner*)

Pulmonary Emboli.—Of 154 cases of death diagnosed as due to pulmonary emboli the diagnosis was confirmed by autopsy in 132 cases. In 22 no embolus was found, whereas in 90 in which emboli had not been suspected clinically, they were found on autopsy; 133 of these cases came from the Surgical Service and the correct diagnosis had been made in 102 cases (32 had not been recognized clinically and 15 could not be confirmed by autopsy). On the Medical Service the correct diagnosis was made in 30 cases, emboli were not diagnosed clinically in 52 and in 7 the diagnosis could not be confirmed on autopsy. Out of the 22 cases of false embolic syndromes the real cause of death was:

	SURGERY	MEDICINE	TOTAL
Number of emboli confirmed by autopsy	133	89	222
Correct clinical diagnosis	102 of 117 =87%	30 of 37 =81%	86%
Not recognized clinically	31 of 33 =23%	59 of 89 =66%	40%

Surgical cases:

Acute pulmonary edema	3
Pulmonary tuberculosis	1
Subacute bacterial endocarditis	1
Cardiac failure	1
Ruptured heart aneurysm	1
Bronchopneumonia	7
Undetermined	1
Total	15

Medical cases:

Mitral disease	2
Cardiac malformation	1
Bronchopneumonia	2
Undetermined	2
Total	7

Clinically the diagnosis of pulmonary embolus was missed in 149 cases and death was ascribed to uremia, myocarditis, cardiac failure, cachexia, etc. It appears that, although false embolic syndromes do occur, they are much rarer than would appear from the literature. On the other hand, the great number of cases clinically not diagnosed *correctly indicates that a pulmonary embolus* not always assumes the classical dramatic picture. An embolus was lodged in the main trunk of the pulmonary artery 104 times and 55 times emboli were found simultaneously in the left and the right branches.—*Quelques reflexions a propos d'une statistique de 222 cas d'embolies pulmonaires mortelles autopsiées a l'Institut d'Anatomie Pathologique de Strassbourg de 1926 à 1936, L. Géry, R. Fontaine & E. Blum, Presse méd., April, 1940, No. 35, 390.*—(*G. Simmons*)

Endobronchial Foreign Bodies.—In order to remove magnetizable foreign bodies from the stomach and tracheobronchial tree a magnet of cast alnico was used. Alnico is an alloy of aluminum, nickel, cobalt and iron.

The magnet is 3.5 cm. in length, 0.5 cm. in diameter and is attached to a Levine tube through which a metal stylet has been inserted. If necessary, an inflating mechanism can be attached to the other end of the Levine tube. The use of the magnet is illustrated by a report of the removal of a hairpin from the stomach of a baby.—*A New Magnet for Foreign Bodies in the Food and Air Passages, M. Equen, J. A. M. A., January 18, 1945, 127: 87.*—(*H. Abeles*)

Bronchogenic Carcinoma in Tuberculosis Hospital.—During a ten-year period, 12 cases of proved primary bronchogenic carcinoma were admitted to the Norfolk County Hospital for Tuberculosis. The most important conclusions to be drawn from these cases were that there are no certain diagnostic features which differentiate tuberculosis and other chest diseases from carcinoma. All symptoms and signs found in suppurative chest diseases or in tuberculosis may be present in malignant disease. The X-ray findings, infiltration, atelectasis and cavitation, are common to all diseases of the lungs. For this reason it is of prime importance to institute bronchoscopy just as soon as carcinoma has been considered in the differential diagnosis. It is unwise to await the result of sputum cultures and guinea pig inoculations, because the time interval between the suspicion of carcinoma and bronchoscopy should be days and not weeks. If bronchoscopy is inconclusive, further diagnostic measures are immediately indicated.—*The Differentiation of Bronchiogenic Carcinoma and Pulmonary Tuberculosis, N. R. Pillsbury & J. D. Wassersug, New England J. Med., March 8, 1945, 232: 276.*—(*H. Marcus*)

Tumor of the Alveoli.—The tumor of the alveolar cells, also called diffuse or multiple primary carcinoma, is extremely rare. Only 40 cases have been described. The *intra vitam* diagnosis generally is lobar pneumonia, miliary tuberculosis or tumor-metastasis. The case described by the author was diagnosed even during the autopsy as bilateral pneumonia. The patient had suffered from a slight cough for several months. During the last fifteen days of his life he had a very severe cough and high temperature. The diagnosis was bilateral pneumonia. The autopsy showed almost complete hepatization of both lungs. The color was a yellowish gray. The mediastinal lymph nodes were small and showed only some anthracosis. The bronchi contained abundant mucopurulent secretion. In the liver several foci of various size, but perfectly round, were found. These also were of a gray-yellowish color. Only this accidental finding gave rise to the suspicion that the process in the lung was malignant. Microscopic examination showed that in the affected regions the alveolar linings were invested by a layer of tumor cells. The tumor cells themselves were atypical and rarely showed mitosis. Their form was from cubic to high-prismatic. They were nonciliated and had a basophilic protoplasma. Nowhere would those cells invade the connective tissue. The nodules in the liver were of exactly the same structure. The neoplastic tissue extended over great parts of the lungs, but no primary tumor was found. The histological structure is definitely distinct from the more common bronchogenic carcinomata. Despite the wide-spread disease of the lungs the extrapulmonary metastases were insignificant, although in this case they allowed the author to make the correct diagnosis. The genesis of these tumors is disputed. No primary focus can be found and probably the disease has multiple primary centres. The majority of the authors accept the theory that the tumor starts from the alveolar epithelium. It has been proved in animal experiments that certain cancerogenic substances can produce atypical neoplastic changes in the alveolar epithelium. There is a certain resemblance to epizootic adenomatosis (jaagziekte), which causes very similar lesions in the lungs of cattle. Its cause is probably a filtrable virus.—*Sobre un caso de tumor de las celulas alveolares del pulmon, F. Wenger, Prensa méd. argent., January 5, 1945, 32: 44.*—(*W. Swienty*)

Carcinoma of Lung.—An analysis is presented of 181 consecutive cases of primary carcinoma of the lung in which operation has been performed over a period of eleven years. Seventy-one cases, or 39 per cent, have been operable, whereas 110 cases, or 61 per cent, were inoperable at the time of exploration. The distribution according to sex showed a six to one ratio in favor of the male. The age incidence did not differ to any great extent from the age incidence of malignant growths elsewhere in the body. The signs and symptoms were, in order of frequency, cough, hemoptysis, pain, loss of weight, hyperpnea, pneumonitis, fever, tightness in the chest. Not only the development of a cough but also changes in the character of a preëxisting cough are significant findings. The pain is usually described as a constant dull ache deep in the chest. The hyperpnea is paroxysmal in character. It may possibly be explained by a plug of mucus occluding a bronchus at the site of a tumor and causing obstructive emphysema. There are no characteristic signs and symptoms of primary carcinoma of the lung but their recurrent nature demands an early, thorough investigation of the respiratory tract. The roentgenogram of the chest is the most important method for the diagnosis of primary pulmonary carcinoma. Positive findings were obtained in all cases. They may be caused by the tumor itself or by secondary changes such as atelectasis, bronchiectasis, pneumonitis or abscess. Next to the roentgenogram, bronchoscopy is the most important examination. It revealed a bronchogenic carcinoma confirmed by biopsy in 61 per cent of the patients in this series. If the growth cannot be seen, fixation or deformity of the bronchial tree may give valuable information. There were no untoward effects due to the bronchoscopies. Bronchography may be useful to demonstrate occlusion of a bronchus which does not produce a shadow in the roentgenogram. It was not necessary to resort to bronchography in this series. Aspiration biopsy should not be used since it is generally uninformative and very dangerous. Exploratory thoracotomy was performed in 25 cases in which no definite diagnosis could be made by other means. If palpation or observation do not reveal the true nature of a lesion excision of the involved area should be carried out. There was no complication following this procedure. The pathological examination revealed two types of lesions. The majority of the tumors occurred at or adjacent to the hilum. They were of bronchogenic origin. They grew either intrabronchially into the lumen of the bronchus and toward the trachea arising from the bronchial mucosa or they grew along outside of and around the bronchus originating extrabronchially in the wall of a smaller bronchus and breaking through its wall. The minority of the tumors occurred in the periphery of the lung. They grew centrifugally apparently arising in the alveolar lining cells. The first symptoms produced by a primary carinoma of the lung depend upon the type of tumor. The peripheral tumors may remain asymptomatic until they invade the pleura, the chest wall or the brachial plexus. The hilar tumors of the intrabronchial type will cause respiratory symptoms, the ones of the extrabronchial type will interfere with the function of the mediastinal structures. In 70 per cent of the patients on whom pneumonectomy was performed there were metastases to the bronchial and tracheal lymph nodes which were removed together with the affected lung. In 110 cases that were found to be inoperable at the time of exploration, in addition to regional metastases there were metastases in other organs. Microscopically, 64 per cent of the tumors were classified as flat or squamous cell carcinoma and 36 per cent as adenocarcinoma; the latter group included the adenocarcinomata, oat cell types and cylindric cell carcinomata. The prognosis as to the length of life was better in the group of patients with a tumor of the flat or squamous cell type. The only efficacious treatment of primary carcinoma of the lung is pneumonectomy with removal of the regional lymph nodes. Medical therapy is only palliative, radiation

therapy is of no benefit. During a period of eleven years 71 pneumonectomies were performed for carcinoma of the lung. The postoperative mortality rate was 21 per cent. With the improvement of technique and the use of chemotherapy a decrease of the postoperative mortality rate can be expected.—*The Present Status of the Surgical Treatment of Primary Carcinoma of the Lung, W. F. Rienhoff, Jr., J. A. M. A., December 30, 1944, 126: 1123.*—(*H. Abeles*)

Primary Lung Cancer.—In the Mexico City General Hospital a special service for nontuberculous diseases of the chest has been founded. Systematic X-ray examinations, iodized oil studies and bronchoscopy are done in every patient between 40 and 60 years of age who presents symptoms of chronic nontuberculous bronchopulmonary disease. Occasionally, thoracocentesis and biopsy have been necessary to establish the diagnosis. Within three years 48 cases of pulmonary carcinoma were detected. The diagnosis has been confirmed either by biopsy or by autopsy. Among the 48 cases, 36 (75 per cent) were men and 12 (25 per cent) were women. The ages ranged from 33 to 68 years with an average of 53 years. The younger patients showed extensive and early metastasis which led rapidly to the fatal conclusion. The only symptom of one 33 year old patient was pain in the right arm produced by pressure on the brachial plexus by early metastasis in the supraclavicular ganglia. The primary neoplasm was found in the mucous membrane of the right upper bronchus. Death occurred after four months. Older patients showed a relative tolerance to the disease. A man of 64 years had signs and symptoms of bronchial carcinoma seven years prior to his admission. But thorough exploration of the mediastinum during operation did not reveal any metastasis. The localization of the primary neoplasm was in the right hemithorax in 30 cases (63 per cent), in the left chest in 17 cases (35 per cent) and in the trachea in one case. In 36 cases, the site of the tumor was established by bronchoscopy; 16 cases showed localization in the right lower bronchus, 18 in the right upper bronchus, 10 in the left lower bronchus, one in the left upper bronchus and one case in the trachea. Three cases of high localization and early supraclavicular metastasis were characterized by pain in the shoulder, Horner's syndrome, atrophy of the muscles of the hand and destructive processes in the ribs or in the neighboring vertebrae. Etiologically tobacco abuse is of importance, as it was found that all cases presented by the authors were heavy smokers. Bronchial carcinoma does generally not produce early metastasis. The time for surgical intervention (between the beginning of the disease and the appearance of distal lesions) is therefore long. Metastases takes place via lymphatics or blood-stream. The latter explains the frequency of cerebral metastasis in cancer as well as in pulmonary abscess. The localization of the metastases was generally in the mediastinum and supraclavicular lymph nodes, in the liver and in the brain. There was generalized carcinomatosis in one case. The majority of the cases had come to the authors after they had been treated for pulmonary tuberculosis for a long time. The main symptoms which made it possible to make the correct diagnosis were persistent cough with blood-tinged sputum or repeated hemoptysis. Only 30 per cent of the cases did not have blood in the sputum. Dyspnea and pain, slight afternoon temperature are almost constant symptoms and are explained by the presence of pulmonary suppuration, bronchiectasis or abscess cavities. The examination shows atelectasis or pulmonary consolidation with exudative bronchoalveolitis, destruction of parenchyma with suppuration, dilatation of the bronchi and pleural thickening. All operative and autopsy specimens showed that the tumor started in the bronchial mucosa, generally at the branching point of a primary or secondary bronchus. Bronchoscopy showed two main types of tumor: a polypous tumor which obstructed the bronchial lumen or an infiltrating tumor with irregular thickening of the bronchial wall and concentric stenosis. The

differential diagnosis has to exclude tuberculosis, syphilitic mediastinitis, scars from chest wounds, congential stenosis or benign tumor. A biopsy by lung puncture has been done four times and has given positive results in two: one sarcoma and one carcinoma. The prognosis is always fatal. Deep X-ray and radium treatment were of no benefit. Endoscopic resection is of no avail, as the endobronchial portion of the tumor is only small in comparison with the peribronchial process which cannot be removed. Pneumonectomy or lobectomy are the operations of choice. They should be done early. The increase of pulmonary cancer is due, in the authors' opinion, to improvement in diagnostic methods and not to factors depending upon modern civilization.—*Nuestra esperiencia en el cancer primitivo pulmonar, J. Gonzalez M. & A. Celis, Rev. mex. de tuberc., May–June, 1944, 6: 59.*—*(W. Swienty)*

Transthoracic Biopsy in Cancer of Lungs.—The symptoms of early cancer of the lungs are intense cough, bronchial catarrah with mucous hypersecretion, frequent attacks of asthma and dyspnea, repeated and sometimes abundant hemoptysis. Sibilant râles and rhonchi are generally present but may be absent if the tumor is situated in the periphery. The late complications and their symptoms are atelectasis, abscess, suppuration, pleural pain and exudate, compression of the mediastinal structures and distant metastasis. Bronchopulmonary carcinoma may be mistaken for tuberculosis, pleurisy, lung abscess or gangrene. In the absence of pathognomonic X-ray findings these errors are understandable. It is important to make the correct diagnosis early. Malignancy must always be considered if a patient of more than 40 years of age has symptoms of persistent bronchial irritation and pulmonary tuberculosis has been ruled out. For early diagnosis sputum examination, bronchography, bronchoscopy, planigraphy and bronchoscopic biopsy are necessary. Other diagnostic procedures of value are exploratory thoracotomy and aspiration biopsy. There are conflicting opinions about the advantages and dangers of the biopsy by transthoracic aspiration. The authors have not seen any untoward effects in their cases. In all operable cases thoracotomy should be done. Aspiration by biopsy is necessary where the bronchoscopy and the sputum examination give negative results. In the very early stages of bronchopulmonary malignancy, there are not enough diagnostic criteria to warrant an exploratory thoracotomy. In the late stages the tumor may be inoperable due either to its extent or due to metastases. In all these cases the authors use the transthoracic aspiration biopsy. Seven cases are presented. Six were more than 50 years of age and one 36 years. Six had blood tinged sputa, one hemoptysis from the beginning. All had pain in the affected hemithorax. One case simulated a pulmonary suppuration, one a pleurisy and 5 pulmonary tuberculosis. Of the latter, 2 were treated with pneumothorax, one with phrenemphraxis, one with gold salts and one with rest. In these cases no endobronchial lesion could be found. In 6 cases the allergy to tuberculin was low. In all 7 cases the aspiration biopsy proved the diagnosis. Six were epidermoid epitheliomata and one an adeno-carcinoma.—*Canceres pulmonares simulando diversas neumopatias, Su diagnostico por puncion transtoracica, A. Fernandez Conde & R. Meneses Mañas, Rev. cubana de tuberc., October–December, 1944, 8: 571.*—*(W. Swienty)*

Metastatic Cancer.—The roentgenological appearance of lymphatic spread of metastatic carcinoma is characterized by diffuse linear densities and fine miliary nodules involving mostly the lower and central portions of the lungs. In most cases the hilar nodes are invaded and enlarged. As a rule, both lungs are equally affected; sometimes, particularly if the primary tumor is in the lung, the lymphatic spread is limited to, or predominant on, one side. In the absence of known primary carcinoma, the roentgenological diagnosis may be difficult and a number of conditions (miliary tuberculosis, pulmonary edema and

congestion, sarcoidosis, pneumonoconiosis, bronchiectasis, etc.) have to be excluded before arriving at the diagnosis of lymphangitic carcinoma. In 70 per cent of the cases the primary tumor arises in the stomach. It is generally believed that the carcinoma cells reach the hilar nodes through the efferent, and not through the afferent, lymphatics. Of the two lymphatic systems of the lung, the deep (intrapulmonary) and the superficial (pleural), the former is predominantly involved. Macroscopically, the affected lymphatics appear as gray lines, arranged in a mosaic pattern: the bronchi and blood vessels are surrounded by a cuff of tumor. In microscopic sections the lymphatics are dilated and contain metastatic carcinoma cells. In some cases, wide-spread arterial involvement is present. With multiple tumor cell emboli, there is fibroblastic reaction in the adventitia and intimal thickening. The clinical symptoms of lymphangitic carcinosis (dyspnea, cyanosis, cough, cachexia) are frequently so severe as to overshadow those caused by the primary tumor. Occasionally right heart failure sets in. The clinical, roentgenological and pathological findings in 10 cases of lymphangitic pulmonary carcinosis are presented. It seems evident that the roentgenological manifestations are caused by the carcinomatous changes in the lymphatic system.—*Roentgenologic Appearance and Pathology of Intrapulmonary Lymphatic Spread of Metastatic Cancer, H. P. Mueller & R. C. Sniffen, Am. J. Roentgenol., February, 1945, 53: 109.*—*(P. Lowy)*

Hemosiderin Formation in Lung.—Three groups of rabbits were injected intratracheally with homologous blood, hypertonic dextrose solution and a mixture of the two. The lungs were examined after varying intervals. It was found that within four hours after the introduction of whole blood, hypertrophy, hyperplasia and desquamation of the alveolar lining cells occurred, reaching a peak in twenty-four hours and then receding. The red cells were disposed of rapidly, in part and perhaps entirely through the phagocytic activity of the activated alveolar lining cells, and there was no local hemosiderin formation. Hypertonic dextrose alone produced a transitory pulmonary edema and hyperemia for as long as twenty-four hours, with mild stimulation of the lining cells. A mixture of dextrose and blood produced a more pronounced lining cell activation and exudative response than that caused by either alone, and many intact erythrocytes were found in the alveoli after the second day. Hemosiderin was first observed after twenty-four hours as a faint blue discoloration (Gomori stain for hemosiderin) in the cytoplasm of the macrophages, both those free in the lumen and those attached to the septal wall. It gradually assumed a granular character and, by the end of a week, was seen as dark, compact blue masses. After the fourth day most of the intact red cells and free macrophages had disappeared. Those macrophages which remained attached to the septal walls appeared to undergo retrogression in size and were susceptible to reactivation as long as fourteen days after an episode of phagocytic activity. The hypertrophy and phagocytic activity of the alveolar lining cells apparently do not constitute an irreversible change so long as they retain their septal attachments.—*Formation of Hemosiderin in the Lungs: An Experimental Study, G. Strassmann, Arch. Path., August, 1944, 38: 76.*—*(D. G. Freiman)*

Thoracic Sarcoidosis.—The cutaneous lesions known as lupus pernio and the systemic disease known as sarcoidosis were first described as a clinico-pathological entity by Schaumann, who also called attention to the similarity between the X-ray appearance of chronic miliary tuberculosis and certain cases of sarcoidosis. It is now recognized that the histological unit of sarcoidosis is the "hard tubercle." It has been repeatedly shown that sarcoid tissue ultimately replaces lymphoid structures, and its predilection for the lymphoid tissue in the interlobar septa accounts for the diffuse streaking seen in the pulmonary roentgenogram. There may be extensive in-

filtrations and minimal or absent physical signs and symptoms. In some cases the radiographic shadows diminish or even completely disappear while in others they may persist without apparent change for many years. It is possible that a large number of cases of chronic or healed *miliary pulmonary tuberculosis belong in this group.* The average interval required for the lesions to disappear completely or almost completely is twenty-two months. After the clearing of the pulmonary infiltrations, recurrences are rare, but the appearance of new lesions, as hilar adenopathy is decreasing, is common. The heart is not infrequently involved, and there may be right heart failure due to diffuse pulmonary sarcoidosis. While the recognition of myocardial and pericardial lesions is often impossible during life, numerous cases of cardiac enlargement have been described which in the absence of murmurs or hypertension may represent myocardial sarcoidosis. Two cases in the authors' group developed cardiac enlargement while under observation. Twelve cases are presented, illustrative of the varied, but most frequent roentgenological appearance of thoracic sarcoidosis. Only cases confirmed by histological examination are included. For convenience they are grouped according to the roentgenological appearance when first seen. These groups demonstrate the chronicity and variable degrees of progression of the disease and also the definite tendency to complete healing; the hilar adenopathy and pulmonary infiltration of strand-like, reticulated, miliary, nodular or confluent type; the recession of hilar adenopathy with the extension of parenchymal infiltrations and vice versa. Involvement of the heart is suggested in 2 cases by the changes in size and shape of the cardiac shadow. Because of the roentgenological resemblance between sarcoidosis and other conditions, especially tuberculosis, diagnosis from X-ray studies alone is not justified. Histological findings should be the basis of diagnosis.—*Thoracic Manifestations of Sarcoidosis, S. S. Bernstein & M. L. Sussman, Radiology, January, 1945, 44: 87.—(G. F. Mitchell)*

Metabolism in Boecks' Sarcoidosis.—Sarcoidosis is considered a generalized, systemic disease. The skin lesions were the first to be described. Schaumann was the first to see all the manifestations as one disease, to realize that it may exist without the skin lesions, and that lymph nodes, tonsils, spleen, bone marrow and lungs are frequently involved. Recently pulmonary lesions, with or without lymph node enlargement, have been reported that have characteristics in common. Pinner reported similarities in many cases diagnosed as Boecks' sarcoidosis, uveoparotid fever, Mikulicz's syndrome, *osteitis tuberculosea multiplex cystoides* and a number of disseminated and lymph node lesions. The etiology of the condition remains unsettled. Pinner regards sarcoidosis as a form of "noncaseating tuberculosis." Pathologically the typical lesion is the so-called "hard tubercle" consisting microscopically of a collection of large, pale-staining, polygonal epithelioid cells which is usually sterile on culture and animal inoculation. The lesions may remain unchanged for long periods of time and heal by fibrosis and hyalinization. The signs and symptoms vary with the location and extent of the lesions, but include malaise, weakness, drowsiness, anorexia, weight loss, low grade fever, night sweats, dry mouth and generalized aches and pains. Laboratory studies may reveal a leucopenia with a relative increase in the monocytes or eosinophiles and with the red blood count below normal. Metabolic studies have revealed an elevation of the serum protein with a reversal of the albumin-globulin ratio. Harrell reported the blood calcium at or above the upper limits of normal in 6 of 11 cases and phosphatase levels above normal in 7. The prognosis is disputed, and the treatment is symptomatic. Three cases are reported by the writer in which metabolic studies were made. Two of the cases had uveoparotitis. Numerous laboratory and metabolic studies were made in the

hope of contributing toward the etiology of sarcoidosis. Guinea pig inoculations were negative. Antigen prepared from lymph nodes of one patient gave no positive intracutaneous reactions and no "anticutins" could be demonstrated. Only 8 proved cases of sarcoidosis of the heart have been reported, though there probably have been many others, and, while previous unrecognized rheumatic fever could not be definitely excluded, it is thought possible that the prolonged P-R interval of one patient might be an indication of sarcoid lesions in the heart of this patient. Leucopenia and eosinophilia were present in all the cases reported here. The red blood count and the hemoglobin were normal. The serum alkaline phosphates were elevated in the 3 cases, but the serum acid phosphates were not affected. The blood calcium, phosphorus, cholesterol, glucose and urea showed normal values.—*Sarcoidosis of Boeck, B. M. Stuart, Am. J. M. Sc., December, 1944, 208: 717.*—*(G. F. Mitchell)*

Pleuropulmonary Changes in Acute Nephritis.—In certain cases of diffuse glomerulonephritis, also called "war nephritis" or "trench nephritis," acute bronchopulmonary changes may present the main symptoms and completely overshadow the nephritis. The authors present 12 cases of diffuse, acute glomerulonephritis and one case of subacute hemorrhagic nephritis in which the pleuropulmonary complications were the foremost symptoms. These changes were pulmonary congestion in 8, cortico-pleuritis in 2, and broncho-alveolitis and bronchopneumonia in one case each. In all observations the renal and the pulmonary symptoms appeared almost simultaneously. The onset was always preceded by inflammation of the tonsils and the pharynx which, in the author's opinion, was the cause of the nephritis. The pathological changes of the lungs and the pleura presented no peculiarities and resolved in a very short time, except for one case (of hemorrhagic nephritis) who died. All symptoms were exclusively or predominantly in the base of the lungs. In the 2 cases of pleuritis the pleural fluid proved to be an exudate. This is of importance, since in nephritis with general edema frequently a transudate is found in one or both pleural cavities. The tonsillitis is the cause of both, the nephritis and the pleuropulmonary pathology. The pathogenic mechanism, however, is different; direct action of the germs in the lungs, and allergic response to bacterial toxins in the kidneys. The *Streptococus hemolyticus*, cause of the nephritis, is associated with pneumococcus, staphylococcus, *Micrococcus catarrhalis*, etc., which produce the pulmonary changes. The treatment is purely supporting. In 2 cases sulfanilamide was well tolerated and effective. The prognosis of the nephritis is not aggravated by the pleuropulmonary complications. — *Alteraciones pleuro-pulmonares en las nefritis agudas, R. Q. Pasqualini & M. C. Lascalea, Rev. Asoc. méd. argent., November 30, 1945, 58: 1074.*—*(W. Swienty)*

Pulmonary Changes in Malignant Hypertension.—The pulmonary findings in malignant hypertension are generally considered as due to passive pulmonary stasis caused by the changes of the heart. The authors believe that some of the changes in the lungs have to be interpreted as congestion or edema due to hyperazotemia. They describe 4 cases of malignant hypertension, in which the blood-urea was between 2 to 3 g. per cent. All had subcrepitant fine râles at the base or the middle portion of the lung, more frequently on the right side. The X-ray picture showed an irregular basal or central density, often bilateral, decreasing towards the periphery. This can lead one to believe that large nodules or inflammatory changes are present. The pulmonary changes in cardiac disease, especially left-sided heart failure, occupy the lower half of the pulmonary field, whereas the uremic lung always shows parahilar density. Here the X-ray findings may be the only means for a differential diagnosis. Differentiation from tuberculosis is evident

by the clinical and laboratory findings. Increase of the blood nitrogen level in these cases leads to an increase of the degree of pulmonary congestion, which responds promptly to a decrease of the blood nitrogen. In 8 cases of extrarenal hyperazotemia without hypertension the authors did not find any pulmonary changes.—*Aspectos radiologicos del pulmon en la hipertonia maligna, M. R. Castex & E. S. Mazzei, Prensa méd. argent., December 27, 1944, 31: 2637.*—(*W. Swienty*)

Pulmonary Changes in Retroperitoneal Tumor.—The author describes the case of a 30 year old woman who suffered from persistent elevation of temperature for seven years. An X-ray picture showed a left infraclavicular infiltrate and induration of the entire upper left lobe and marked accentuation of both hilar regions. This infiltration disappeared rather surprisingly from one X-ray examination to the other within a few days. Incidentally, a tumor of almost head-size was found in the left hypochondrium, moving with respiration. This tumor did not cause any symptoms. A pyelogram was taken and a renal tumor was diagnosed which compressed the stomach and the duodenum and shifted the entire upper portion of the intestine to the right, causing gastrointestinal disturbances. The patient suffered several sudden attacks of violent pain in the tumor region followed by cough, dyspnea and suffocation. A chest X-ray revealed an opacity covering the entire lower third of the left hemithorax and some haziness of the remainder of both lungs. Ten cc. of serous, yellow, clear transudate were aspirated. The patient recovered from this attack within four days. An X-ray film at this time showed complete reabsorption of the transudate, leaving only a slight veil-like haziness in the left lower chest. The fluid had completely disappeared but for a small amount in the left costophrenic angle. The author made the diagnosis of acute pulmonary edema due to "retroperitoneal paranephritic tumor." The possibility of acute dilatation of the left ventricle with exudation was also kept in mind. The patient then suffered another attack of dyspnea and cough, at which time an operation was done. A large tumor was found and a biopsy done. The tumor first gave the impression of a sarcoma and seemed to start from the capsule of the left kidney. Microscopic examinations showed that it was a pseudomucinous cystadenoma, possibily originating from Muller's duct. The patient died two weeks after the operation from a new attack of pulmonary edema. The pathological mechanism is explained by the diminished capacity of the veins in the abdomen due to the pressure and extent of the tumor and by the increased venous return. The author believes with Laubry and Doumer that the abdominal venous net acts as a reserve space and presents a security coefficient in case that the blood volume augments. In this case the blood volume did not increase, but the capacity of the security outlet diminished. The pulmonary capillaries were under a hypertension by the increased venous return. As they are separated from the atmospheric air by a thin membrane only, the alveoles are very easily filled with serosanguineous exudate. Also, it was evident from the microscopic examination that at the time of the crisis the tumor increased greatly in size due to massive interstitial hemorrhage. This in turn caused another decrease in the venous net of security.—*Comprobaciones quirurgicas del mecanismo patogenico de una imagen pulmonar fugaz, C. W. Gröbli, Prensa méd. argent., January 19, 1945, 32: 114.*—(*W. Swienty*)

Rupture of the Main Bronchus.—A case of rupture of a main bronchus without lesions of the thoracic cage is described. The patient survived the accident and the diagnosis was established by tomographic studies. Rupture of the main bronchi in the closed thorax is a rare occurrence. It is most frequent in young individuals, and the cause is mostly a crushing force (wheels of a vehicle), acting in antero-posterior direction. Fractures of ribs, of the clavicle, or of the sternum may be associated, but the external lesions may be insig-

nificant. A complete section of the bronchus occurs, with tear of the bronchial vessels and of the pleural covering of the hilum. In cases surviving the accident there is fibrous healing of the two stumps of the ruptured bronchus, retraction of the corresponding lung, overdistension of the contralateral lung and shift of the mediastinal organs. The most probable mechanism causing this lesion is a shortening of the antero-posterior diameter due to the crushing force and consecutive widening of the transverse diameter. The lungs closely follow the distending chest-wall until the bronchi tear. An increase in endobronchial pressure caused by spasm of the glottis may represent a contributing factor. When death does not follow immediately, the clinical picture is extremely grave and is characterized by dyspnea, cyanosis, shock, pain, hemoptysis, emphysema, pneumothorax and hemothorax. Treatment consists in relief of pain, deflation of hypertensive pneumothorax, repair of blood-loss. Sometimes exploratory thoracotomy or pneumonectomy is indicated.—*Ruptura de grandes bronquios en torax cerrado, O. A. Vaccarezza & A. A. Raimondi, An. Cáted. de pat. y clin. tuberc., 1943, 5: 76.*—(*L. Molnar*)

Lung Picture in Cardiac Insufficiency.—In cardiac insufficiency the X-ray picture of the lungs may simulate other pathological conditions. The author describes 2 cases in which the manifestations in the lung parenchyma and in the pleura responded to treatment of the underlying cardiac insufficiency. The first case was a woman of 65 years who complained of pain in the lower right chest, cough and occasional bloody sputum for the past six months. There was a soft, blowing murmur over the apex and a systolic murmur over the right base of the heart. Blood pressure was 160/100. Fluoroscopy showed a uniform opacity over the inferior third of the right hemithorax. The diaphragm was fixed. Within the right hilum a round, orange-sized shadow with blurred borders was seen. The electrocardiogram was normal. Differential diagnosis was pulmonary neoplasm, cardiac insufficiency or pulmonary infarct. After fifteen days of treatment with digitalis the lesions in the right lung field had almost completely disappeared. The digitalis treatment was considered as conclusive for the final diagnosis, which was cardiac insufficiency (despite the normal electrocardiogram). The second case was a 61 year old man who complained of dyspnea and of edema of the legs for one year. A soft systolic murmur was heard over all valves of the heart. There was extrasystolic arrhythmia. The blood pressure was 120/90, the pulse 98. There was a slight dulness over the base of the right lung and moist, crepitant râles over both lung bases, but especially over the right. The liver was markedly enlarged. The X-ray film showed a shadow within the region of the interlobar fissure on the right with perfectly clear borders and a small hydrothorax of the right base. This was diagnosed as interlobar pleurisy. The lesion disappeared on digitalis treatment. The author states that exudative lesions of the lungs or pleura may be simulated by cardiac insufficiency, that even with a normal electrocardiogram and a normal heart size cardiac disease should not always be excluded. In case of doubt, a fifteen-day treatment with digitalis is indicated.—*Imagenes pulmonares en la insuficiencia cardiaca, D. Fernandez Alfaro, Rev. cubana de tuberc., October–December, 1944, 8: 625.*—(*W. Swienty*)

Composition of Pleural Gas.—The authors determined the carbon dioxide-oxygen percentages in the pleural cavity of 76 patients with a therapeutic pneumothorax. In uncomplicated pneumothoraces the gas in the pleural space showed a CO_2 content ranging from 5.5 to 7.5 vol. per cent and an O_2 content of 2.0 to 4.5 vol. per cent. Following a pneumothorax refill stabilization occurred within forty-eight hours. In patients whose pneumothorax was complicated by a pleural effusion, the oxygen content of the pleural gas ranged from 0 to 1.15 vol. per cent. CO_2 values were fairly constant (9 to 12 vol. per

cent) in pure tuberculous effusions whether serous or purulent but varied from 7.5 to 18.7 vol. per cent in mixed infections. When a fistula without effusion was present the findings were characteristic: the CO_2 content was less than 5.5 vol. per cent and the O_2 more than 6.5 vol. per cent. An effusion complicating the fistula was always accompanied by a CO_2 content of more than 1 vol. per cent. A pneumonolysis had been done in 19 of the 27 patients with a fistula and pleural effusion. The diagnosis of fistula was confirmed in 5 of 8 patients who were examined postmortem.—*Gases pleurales y diagnóstico de la fístula pleuropulmonar, A. Soubric & F. Labourt, An. Cátcd. de pat. y clin. tuberc., December, 1948, 5: 277.*—*(R. Kegel)*

Gas Analysis in Bronchopleural Fistula.—The modern studies on diffusion and absorption of gases in body cavities are reviewed particularly the clinical application of gas analysis in the diagnosis in bronchopleural fistulae. The gas studies of the authors, in cases of pneumothorax with or without effusion, in presence or in absence of bronchopleural fistula, gave results identical to those obtained by Coryllos and Matsuzawa in similar circumstances. It seems noteworthy that bronchopleural fistula was found very often shortly after pneumonolysis. Repeated analysis of the pleural air is a reliable method in the diagnosis of bronchopleural fistula and deserves to be adopted as a routine investigation.—*La absorbcion de los gases en las cavidades del organismo: Diagnostico de la fistula pleuropulmonar, A. Soubric & F. Labourt, An. Cátcd. de pat. y clin. tuberc., 1948, 5: 120.*—*(L. Molnar)*

Respiration under Experimental Conditions.—The changes in vital capacity and maximum breathing capacity have been studied in 11 normal individuals submerged in water at different depths. Under these experimental conditions only the respiratory muscles are subjected to strain and consequently the results may be considered as a test of their action. The maximum breathing capacity has shown a much more accentuated progressive diminution than the corresponding values of the vital capacity. At depths over 30 cm. from the surface, parasternal pain was observed, probably at the site of the insertion of the pectoral muscles; 80 cm. below the surface respiration became impossible after one minute, because the expirations were larger than the inspirations. At depths ranging from 30 to 80 cm., in spite of quantitatively sufficient ventilation, dyspnea was noted. Similar results were obtained in experiments causing the subjects to perform expirations against resistance. This series of experiments shows that the reduction of the *maximum breathing capacity is determined* by muscular fatigue which causes diminution in the number of respirations. It is also demonstrated that the sensation of dyspnea is compatible with normal pulmonary ventilation and is caused, in these experiments and in normal activities reproducing similar conditions, by impulses originated in respiratory muscles subjected to excessive strain.—*La capacidad de ventilación pulmonar en condiciones experimentales desfavorables, F. Labourt & A. Lanari, An Cátcd. de pat. y clin. tuberc., 1948, 5: 48.*—*(L. Molnar)*

Inspiratory Tonus in Anoxia.—Methods for plethysmographically recording the volume changes in the cat, and for measuring the chest circumference of the dog during procedures affecting respiration are described. During the reduction of O_2 content of inspired air from that of the atmosphere to about 8 per cent by rebreathing the volume of the cat's chest at the end of expiration increases by about 60 to 70 cc. This is three times the volume of a normal inspiration. During a similar diminution of O_2 in the inspired air of the dog a proportionate increase in expiratory circumference of the chest occurs. After vagotomy the anoxic increase in expiratory volume in the cat is about one-third as great as with the vagi intact. In the dog vagotomy totally eliminates the anoxic chest expansion. Crushing the nerves from the carotid chemoreceptors has little or no effect upon the

reaction. Hypercapnia appears to sensitize the animal to the low O_2 chest expansion reaction, but in the presence of a large excess of O_2 accumulated CO_2 does not produce an increase in the expiratory volume in cats or dogs. In some animals there is a small reduction in chest volume when the expirations become forceful. The human expiratory chest volume has been shown to enlarge during dyspnea. The suggestion that respiratory training to exhale more completely may be valuable to people at high altitudes is briefly discussed. (Author's Summary)—*Inspiratory Tonus in Anoxia, A. S. Harris, Am. J. Physiol., January, 1945, 143: 140.*—(*G. C. Leiner*)

Acute Abdomen Simulated by Pleuropulmonary Perforation.—A spontaneous pneumothorax caused by perforation of the visceral pleura may simulate under exceptional conditions an acute surgical abdomen. The symptoms are sudden abdominal pain which is severe and stabbing, vomiting, boardlike rigidity of the abdominal muscles, intestinal paresis, rapid pulse, profuse sweating and polypnea. If these symptoms are complicated by a high leucocytosis and marked shift to the left, it is understandable that a diagnostic error can be made and surgery performed. A small marginal pneumothorax may not even be detected in the X-ray film. The authors present 2 cases. In one the white count was 37,500 and went down to normal after aspiration of air. The tentative diagnosis had been perforated gastric ulcer until the X-ray film revealed a spontaneous pneumothorax. In the other case in which a laparotomy was performed the leucocyte count was 31,500 and rose to 68,500. The preoperative diagnoses had been: perforated gastric ulcer, perforation of the gallbladder, subphrenic abscess, liver abscess, acute appendicitis or acute pancreatitis. No abdominal abnormality was found. This case had been treated with a therapeutic pneumothorax and only after surgery a pleuropulmonary fistula with effusion was diagnosed. The mechanism of the abdominal pain in spontaneous or tension pneumothorax is still disputed. It may be caused reflexly by sudden compression of the mediastinum, by irritation of the sympathetic or pneumogastric nerves, by a viscero-motor reflex, by irritation of the inferior intercostal nerves which also innervate the proximal portion of the abdominal muscles, or by referred pain.—*Sindrome abdominal agudo por perforacion pleuropulmonar, A. F. Conde & E. A. Lastra, Rev. cubana de tuberc., July–September, 1944, 8: 504.*—(*W. Swienty*)

Spontaneous Pneumothorax.—Two cases of spontaneous pneumothorax due to metastatic sarcoma are reported. The first case was that of a 19 year old youth with a recurrent fibrosarcoma arising from the tendon sheath of the left *flexor pollicis longus*, for which the arm was amputated. Six months later the patient developed a chill and upper respiratory infection followed by dyspnea, right pleuritic pain and cough with bloody sputum. A roentgenogram of the chest revealed extensive metastases to both lungs and a right pneumothorax. Two weeks later, following some symptomatic improvement, he suddenly became markedly dyspneic and cyanotic, dying twenty-five minutes later. An autopsy revealed extensive metastatic fibrosarcoma of both lungs with bilateral pneumothorax. The second case was that of a 20 year old youth with an osteogenic sarcoma of the left femur for which a hip joint disarticulation was performed. A Welch bacillus infection followed, and the wound healed slowly. Seventeen months later a roentgenogram of the chest revealed metastatic foci, and two courses of roentgen therapy were administered. A right hydrothorax developed, accompanied by chest pain and cough. Several taps were performed revealing bloody fluid. Several weeks later he suddenly became dyspneic and was found to have a left pneumothorax. In spite of continuous suction drainage, he became rapidly worse and died. An autopsy revealed extensive metastatic osteogenic sarcoma of the lungs. The left lung was collapsed. Air injected into the trachea

escaped through a necrotic nodule in the left upper lobe. The rupture of a necrotic tumor nodule into a bronchus and into the pleural space, resulting in a small bronchopleural fistula, seems to be the most likely explanation for the occurrence of spontaneous pneumothorax in these cases. Such a complication is rare as evidenced by the lack of similar cases reported in the recent English and American literature.—*Pneumothorax Due to Metastatic Sarcoma: Report of Two Cases, T. F. Thornton & R. R. Bigelow, Arch. Path., May, 1944, 37: 334.*—*(D. G. Freiman)*

Pleurisy Caused by Brucellosis.—Physicians are more conscious of the wide spread of brucellosis since Gould and Huddleson have estimated that at least 10 per cent of the population of the U. S. A. have the disease and 1 per cent is clinically ill with it. From the various symptoms which can be caused by brucellosis the author has selected pleurisy. Patients affected with brucellotic pleurisy present cough and expectoration, pleural pain, subfebrile temperatures, loss of weight and secondary anemia. Four cases are discussed in which a pleurisy with effusion was present. The agglutination test was always positive in concentrations of 1:100 to 1:500. On treatment with specific vaccine the fluid completely disappeared in a relatively short time. The author considers it as very possible that some cases of brucellosis have been mistaken for tuberculous pleurisy, typhoid fever, rheumatic disease, nonpurulent pneumonia, syphilis or other infections. It is understood that tuberculosis has to be ruled out in every case, even if the agglutination test is found positive for Malta fever in low titres. The effusion can be either serofibrinous or hemorrhagic due to the tendency for hemorrhages which is one of the symptoms of brucellosis. It is suggested that this hemorrhagic diathesis is caused by a lack of ascorbic acid as it disappeared promptly with the administration of vitamin C. The prognosis is good. The fluid disappears without any sequelae. To ascertain the diagnosis of brucellosis the history of the patient and the existence of infected animals or other persons has to be searched for. The laboratory tests include the agglutination tests in the blood, in the cerebral-spinal fluid and in the effusion, the intracutaneous reaction and the blood culture from the pleural fluid and spleen. The agglutination tests should be regarded as positive even in as low a titre as 1 to 20 to 1 to 50. Finally, the author states that in each case of brucellosis a thorough study of the lungs and of the pleura by clinical and X-ray examination should be made routinely.—*Pleuresias brucelosicas, Contribucion a su estudio, I. Maldonado-Allende, Rev. Asoc. méd. argent., December 15, 1944, 58: 1107.*—*(W. Swienty)*

Hemothorax.—Although many theories have been advanced for the presence of clotting in some hemothoraces and its absence in others, no one theory will satisfy all questionable points. No matter what the pathogenesis of clotting may be, in the present series of 750 chest injuries, 52, or 70 per cent, had hemothoraces, and infection was present in 30 per cent of hemothoraces. Only 9 per cent of all hemothoraces were clotted. The incidence of clotting in hemothoraces rose sharply during 1944, when penicillin became more generally available. This led to the speculation whether penicillin, if used prophylactically without previous aspiration of blood, might be responsible for the clotting, although no such *in vitro* effect has been observed. Clotted hemothorax may be massive or loculated. The diagnosis may be suspected from the X-ray findings, but repeated unsuccessful aspirations usually prove its correctness. Although blood can be absorbed freely from the pleural cavity, and small, and sometimes even large hemothoraces may be resorbed, the usual course of events is the laying down of a thick layer of fibrous tissue on the parietal and visceral pleura. This prevents reëxpansion of the lung and is responsible for the "frozen chest" in which the lung loses most of its respiratory function. Evacuation of the clot with decortication of the lung has been found to be the most satisfactory treatment. Usually the entire lung must be de-

corticated, and only in small hemothoraces localized decortication will do. The operation is done through a thoracotomy with resection of part of the sixth posterior rib. The fibrous layer on the parietal pleura is two to three times as thick as on the visceral pleura and needs thorough removal as well. Suction drainage postoperatively, through two tubes, is of great importance. One tube is put into the upper chest, preferably into the second posterior intercostal space, to prevent residual pockets in the upper chest. A second tube is put low into the posterior chest at the conventional site. Negative pressures of 5 or 6 cm. of mercury are used. The results of suction drainage are far superior to underwater drainage in that lung expansion is more rapid and more complete. The identical treatment has also been applied to infected clotted hemothoraces and to closed and previously drained empyemata. It was found that decortication and suction drainage was a far more satisfactory treatment for these conditions, and expansion of the lung was the rule. In some cases expansion of the upper lobe only was obtained, and the empyemata became confined to small pockets which healed more promptly than a total empyema space would have. Closed empyemata are sterilized with penicillin before treatment, and infected hemothorax clots and open empyemata have been successfully treated with penicillin drip for twelve to twenty-four hours. The solution is administered through the two tubes later to be used for suction. Penicillin has been of great value in sterilizing pleural cavities infected with streptococci and staphylococci, but after decortication organisms are apt to recur. For this the penicillin drip is valuable, and the organisms tend to disappear as lung expansion proceeds. Coliform organisms, *B. proteus*, and *B. pyocyaneus* tend to disappear spontaneously after decortication and suction drainage, and *Clostridia* do not persist in adequately treated cases.—*Decortication in Clotted and Infected Hemothoraces, C. P. Thomas & W. P. Cleland, Lancet, March 17, 1945, 248: 327.*—(*H. Marcus*)

Traumatic Hemothorax.—When blood escapes into the pleural cavity rapid clotting takes place. Frequently, however, the clot remains liquid because the cardiac and respiratory motions defibrinate it and deposit fibrin on the parietal and visceral pleura. This is the case when bleeding occurs at a slow rate. When bleeding is rapid a solid clot forms which defies aspiration. Most traumatic hemothoraces yield to repeated early aspirations. If aspiration is not done early, or if a solid clot forms, surgical removal of the clot is indicated. This is done through a posterolateral incision, the exact location depends on the location of the clot. The sixth, seventh or eighth interspaces are most commonly used. Usually a well organized hematoma is encountered. Removal of this and its wall reveals a relatively normal pleura, and even at operation the lung will be seen to reëxpand partially, and the diaphragm will resume more nearly normal movements. Complete reëxpansion of the lung is effected with a short period of underwater drainage postoperatively. The results of such treatment are almost uniformly good permitting men to return to active duty within a short time. Untreated hemothorax results in a chronic respiratory disability. Low grade fever, persistent chest pain, anemia, dyspnea and asthenia are the rule. The decrease in respiratory function is striking. The affected hemithorax is partially immobilized, and the unaffected lung undergoes compensatory emphysema. Patients with untreated hemothorax cannot return to active duty.—*Traumatic Hemothorax, F. P. Coleman, Arch. Surg., January, 1945, 50: 14.*—(*H. Marcus*)

Hemothorax.—When blood is liberated into the pleural cavity by trauma, three immediate harmful effects take place: blood loss, pleural irritation and an expanding, space occupying lesion in the chest. Although no clotting is frequently observed in a hemothorax, deposition of fibrin on the lung, the parietal pleura and the diaphragm is usually prompt. The fibrin deposited on the visceral

pleura changes into fibrous tissue within a matter of days or weeks, and, unless prompt steps are taken to prevent this occurrence, the lung may become bound down by a rigid coat of fibrous tissue. The irritation which results from the presence of blood in the pleural davity, which here acts as a foreign body, causes the outpouring of a serous effusion. This augments the respiratory distress. Bleeding into the pleural cavity may come from the lung, from the chest wall or from the abdomen. Bleeding from the lung stops spontaneously and is rarely severe. Bleeding from the chest wall is often persistent, especially when it comes from an intercostal artery or the internal mammary artery. When the right leaf of the diaphragm has been penetrated by a missile and the foreign body has lodged in the liver, blood from the liver is apt to be pumped into the right pleural cavity with the respiratory movements of the diaphragm. Hemothorax is easy to diagnose if it is kept in mind that displacement of the mediastinum is a late sign that should not be awaited to make a diagnosis. Shock, pain, and dyspnea are early signs. The diagnosis is made by X-ray examination, but the patient must be in a sitting position. Lateral films are important. Even with these a hemothorax rarely gives the sharp straight outline which an empyema and other pleural effusions are apt to give. The margin of the hemothorax blends almost imperceptibly with the surrounding lung tissue, and a pulmonary hematoma may be mistakenly diagnosed. All hemothoraces should be treated promptly by aspiration, preferably within twenty-four hours. It is true that some hemothoraces resorb without treatment leaving no disability, but one cannot predict which ones are going to react this way. The only way in which poor late results can be avoided is by prompt immediate treatment of all cases. The majority of cases respond to repeated simple aspirations. As time goes on, aspirations become more difficult because of clots and fibrin, and a mistaken diagnosis of clotted hemothorax is often made. When hemothorax is very massive and bleeding continues under observation, it is best to evacuate blood, clots and fibrin through a thoracoscope. Air which enters the pleural cavity during this process should be aspirated. If bleeding continues slowly for many weeks, intercostal thoracotomy should be performed, the contents of the pleural cavity should be evacuated and the bleeding point secured, if possible. Even if this last procedure cannot be done, bleeding frequently stops following thoracotomy. Clotted hemothorax should be treated by thoracotomy and removal of the clot and decortication as soon as the diagnosis has been made. Retained foreign bodies should also be evacuated early, providing there are not too many and they are not located near the hilum.—*Hemothorax, N. R. Barret, Lancet, January 27, 1945, 248: 103.—(H. Marcus)*

Hemothorax.—When blood escapes into the pleural cavity it may remain liquid for a long time. This is due to the fact that, although clotting occurs, the clot is defibrinated through the mechanical action of the cardiac and respiratory movements. Fibrin is deposited on the visceral and parietal pleura, but the bulk of the contents of the cavity remains liquid. Early and regular aspirations reveal the fact that the hemoglobin content of the hemothorax is about 30 to 40 per cent less than the hemoglobin content of the blood. Repeated daily aspirations show that the hemothorax is quickly diluted by the outpouring of a serous effusion, and the hemoglobin content falls quickly. The fibrinogen content, on the other hand, rises progressively. The marked outpouring of fluid several days after wounding sometimes leads to the erroneous impression that bleeding is continuing. Aspiration quickly decides this question. A properly treated case should be dry after the fifth or sixth aspiration. If treatment has been delayed and fibrin has a chance to form, complete reëxpansion of the lung cannot take place. Evacuation of fibrin and clot through an intercostal incision must then be done, or in more severe cases thoracotomy and decortication of the lung must

be done to secure reëxpansion.—*Hemothorax, T. H. Sellors, Lancet, February 8, 1945, 248: 143.*—(*H. Marcus*)

Postoperative Empyema.—A study was undertaken to determine the value of penicillin prophylaxis in the prevention of empyema following transsection of the bronchi for lobectomy or pneumonectomy. Penicillin was administered intramuscularly every two hours daily for one week preoperatively and for two weeks postoperatively; the daily dose was 150,000 units of penicillin. No local application or instillation was used. Forty-eight patients had partial, single or multiple lobectomy or pneumonectomy. Seven patients died shortly after the operation. Forty-one patients were selected for analysis, 21 of them received penicillin prophylactically, 20 patients served as controls. Twenty-one patients had partial or total lung resection for bronchiectasis or multiple lung abscesses; 12 of them, 10 lobectomies and 2 pneumonectomies, were treated with penicillin. None of the 12 patients developed empyema. Nine patients served as controls in the series of suppurative pulmonary infections. All 9 patients developed empyema, 3 of them died. Fifteen patients had partial or total lung resection for tuberculous infection of the lung. Seven of the latter group were treated with penicillin, 2 of them developed tuberculous empyema. Eight patients served as controls, 3 of them developed pyogenic empyema. Five patients operated on for bronchogenic carcinoma had an uncomplicated postoperative course; 2 of them had undergone prophylaxis with penicillin and 3 patients had served as controls. Of the entire series of 20 control patients, 12 developed empyema. All 12 patients were treated with penicillin. Two received local therapy, they recovered promptly but developed fistulas later on. Three received systemic therapy, 2 of them died while one responded promptly. Seven received local and systemic therapy, 2 of them died, 3 showed slight improvement and 2 recovered promptly.—*Use of Penicillin in Prevention of Postoperative Empyema following Lung Resection: Report of a Controlled Study, W. L. White, W. E. Burnett, C. P. Baily, G. P. Rosemond, C. W. Norris, G. O. Favorite, E. H. Spaulding, A. Bondi, Jr. & R. H. Fowler, J. A. M. A., December 16, 1944, 126: 1016.*—(*H. Abeles*)

Mediastinal Emphysema.—Hamman called attention to 3 cases of interstitial emphysema simulating coronary artery disease; other investigators have mentioned the necessity of considering spontaneous mediastinal emphysema in the differential diagnosis of pain in the chest. The author has seen 8 cases in soldiers during the past three years. In 6, left-sided pneumothorax was demonstrated by X-ray. Four cases are reported, and the similarity of the condition to organic heart disease described. Macklin has described spontaneous mediastinal emphysema as occurring experimentally following overdistention of a lobe, the air entering the perivascular sheaths of the pulmonary vessels. The air bubbles gradually coalesce as they dissect their way and finally rupture into the mediastinum. This perivascular tunneling may also impede the circulation. Occasionally air may pass from the perivascular sheaths into adjoining connective tissue and thence to the pleura forming a subpleural bleb. In the mediastinum air tends to follow fascial planes, especially the sheaths of blood vessels. Thus, air may go into the neck, axilla and chest-wall and may also go between the parietal pleura and pericardium. Clinically, spontaneous mediastinal emphysema is characterized by the occurrence of sudden, often alarming precordial or substernal pain, the severity depending upon the degree of distention of the mediastinal tissues. It may radiate to the back, shoulders, neck or down the left arm and may last several hours or several days. Dyspnea, cyanosis and orthopnea may occur, but are not characteristic. The differential diagnosis depends entirely on the clinical examination. Air may be detected in the subcutaneous tissues of the neck and anterior chest-wall; the area of cardiac dulness may be replaced by hyperresonance,

but the pathognomonic sign is cracking or crepitant sounds heard over the precordium synchronous with the heart beat. Pneumothorax is present in some cases. If uncomplicated, there is no evidence of serious constitutional disturbances. The electrocardiogram reveals no significant change. X-ray films of the mediastinum are diagnostic. Diagnosis, however, may be difficult. This condition occurs chiefly in young people. There probably is a temporary functional coronary insufficiency. EKG changes were noted in 3 cases reported. No similar change is reported in the literature. Although not diagnostic, the electrocardiographic abnormality could be easily mistaken for serious myocardial damage. Similar changes have been reported in spontaneous pneumothorax apparently due to rotation of the cardiac axis.—*Spontaneous Mediastinal Emphysema with Pneumothorax Simulating Organic Heart Disease, H. Miller, Am. J. M. Sc., February, 1945, 209: 211.*—*(G. F. Mitchell)*

Pneumomediastinum. — *Processes tending* to produce overdistention of the lung may be associated with pneumomediastinum. Thus, in obstetrical labor, pertussis, obstructive tracheobronchitis, alveolar rupture may occur, with resulting escape of air along the vascular sheaths to the mediastinum. Local conditions, such as congenital deformities of the respiratory system, trauma, infectious processes, may play a part in the pathogenesis of pneumomediastinum. The consequences are varied. Rupture of mediastinal blebs may lead to unilateral or bilateral pneumothorax, or else may cause escape of air along the vessels and thus produce subcutaneous and retroperitoneal emphysema, pneumoperitoneum or even air embolism. Positive pressure in the mediastinum impedes the return flow of blood to the auricles, by compressing the pulmonary and systemic veins. Dyspnea and cyanosis ensue, with distended neck veins and falling blood pressure. The percussion over the heart becomes tympanitic, the sounds distant; there may be a crackling sound, synchronous with systole. In adults, precordial pain is a frequent complaint. Coexisting pneumothorax tends to alleviate the symptoms, by lowering the mediastinal tension. Roentgenologically, air may be seen outlining the margins of the superior mediastinum in the frontal view; in the lateral view which more often gives conclusive results, encapsulated air is present immediately behind the sternum. Treatment consists of oxygen and stimulants, or, in severe cases, aspiration of air. Three cases of pneumomediastinum in newborn infants are reported, all of whom received vigorous artificial respiration of some form. Whether the artificial resuscitation caused the pneumomediastinum, or the latter gave rise to the cyanosis necessitating artificial respiration, is difficult to determine.—*Pneumomediastinum in the Newborn, R. M. Lowman & C. S. Culotta, Am. J. Roentgenol., January, 1945, 53: 7.*—*(P. Lowy)*

Mediastinal Teratoma.—A case is reported of mediastinal teratoma in a 29 year old man admitted to the hospital with cough of three weeks' duration, aggravated by the prone position and worse at night, and swelling of the neck. A 10 by 6 cm. mass was present in the left anterior cervical triangle, displacing the trachea and larynx to the right and extending substernally. The neck veins were engorged and those of the left upper chest and arm dilated. A roentgenogram of the chest revealed a dense homogeneous mass in the upper mediastinum extending into the neck. Biopsy of a lymph node from the left side of the neck showed replacement by sheets and cords of undifferentiated cells with numerous mitoses. A course of roentgen ray therapy (3525 r over a period of seven weeks) produced a regression in size of only 2 cm. The patient died following an episode of dyspnea. An autopsy revealed a hard tumor mass measuring 18.5 x 17.5 x 10.6 cm. extending downward over the pericardium and upward into the neck, surrounding the ascending aorta and part of the arch, but not involving the thyroid or lung. The testis was negative. Microscopic examination of the tumor revealed a matrix of myxomatous and loose fibrous

tissue containing numerous cysts lined with epithelium ranging in type from stratified squamous to columnar and pseudostratified columnar. In other areas there were cells resembling adrenal cortical cells, endometrium and choriocarcinoma. The tumor appears to have arisen from all three germ layers.—*Mediastinal Teratoma, S. J. Wilson & R. Cares, Arch. Path., February, 1945, **39:** 113.—(D. G. Freiman)*

Right Diaphragmatic Hernia.—In a 22 year old girl with the symptoms and signs of pulmonary and intestinal tuberculosis, the chest X-ray examination showed a picture similar to a right hydropneumothorax. The possibility of a pulmonary or pleural suppuration, or of a subdiaphragmatic abscess was considered. A later chest X-ray examination, one month before the patient's death, revealed two semi-circular opacities at the place of the previous "hydropneumothorax." The exact diagnosis was made after death only. The autopsy showed: Caseocavernous tuberculosis of the lungs with general amyloidosis; tuberculous ulcerations of the ileum; partial aplasia of the anterior part of the right diaphragm with herniation of the hepatic flexure of the colon. Right diaphragmatic hernia is found very rarely as compared to the left.—*Hernie diaphragmatique droite, L. Rousseau & M. Giroux, Laval méd., February, 1945, **10:** 89.—(G. C. Leiner)*

Anomalous Pulmonary Veins.—Two instances of anomalous connection between the pulmonary and systemic venous systems, discovered at autopsy, are described. In one of these a vein draining most of the right upper lobe entered the right side of the superior vena cava; in the other most of the tissue of the upper lobe of the left lung was drained by a vein communicating with the left innominate vein. In both cases death was due to cardiac decompensation on the basis of rheumatic heart disease, and no symptoms that might have been attributable to the anomaly were recorded. By comparing the cross-sectional area of all pulmonary veins with that of the anomalous vein, the percentage of oxygenated blood shunted to the right side of the heart was estimated at 26.1 per cent in the first case and 20.1 per cent in the second. Seven cases encountered in the literature not included in a review by Brody (Brody, H.: Arch. Path., 1942, *33:* 221) are briefly summarized.—*Anomalous Pulmonary Veins, C. W. Hughes & P. C. Rumore, Arch. Path., June, 1944, **37:** 364.—(D. G. Freiman)*

Vagotrigeminal Pain Reflex.—The irritation of the vagus in a region where its sensitive fibres are related exclusively to the functions of the vegetative life causes pain in the territory innervated by the trigeminus. These pains are caused, according to the author, by a vagotrigeminal pain reflex. Head studied the relationship between cephalic pain and the diseases of the thoracic and abdominal organs. Though Head advanced the hypothesis that in such cases the afferent stimulus might be conveyed by the vagus, a definite explanation was not given. The author says that there is a vagotrigeminal pain reflex that explains these cases of trigeminal neuritis. A patient with a bronchial fistula is presented in whom pain in the territory of the trigeminus appeared after mechanical or chemical irritation of the bronchial stump. Local anesthesia prevented the development of pain upon irritation. The author emphasizes the following points: In the patient presented the pain was unilateral and homolateral; no exophthalmos, midriasis, marked flushing of the face were noted; no pain was referred in other regions. All these facts indicate that the afferent pathway was not the sympathetic system. The proximity of the bulbar nuclei of these two nerves might explain the possibility of an afferent stimulus conveyed by the fibres of the region influencing the trigeminus.—*Sobre a existencia de um reflexo doloroso vago-trigeminal e de uma neralgia facial broncogenica, A. Amorim, Rev. brasil. de tuberc., May–June, 1944, **93:** 121.—(P. B. Franca)*

Aortectomy.—The first case of a successful removal of an aneurysm of the thoracic aorta

is reported. A 19 year old student complained of fatigue following an episode of "flu." Physical examination revealed a loud blowing systolic murmur audible throughout the chest, best heard over the pulmonic valve area, and tachycardia. The blood pressure in the right arm was 160/72. It was not obtainable in the legs. Pulsations of the intercostal and internal mammary arteries were palpable. Pulsations of the arteries of the lower extremities were weak. The chest film showed an ovoid, nonpulsating mass, 6 by 8 cm, at the left border of the mediastinum at the level of the fifth, sixth and seventh vertebrae. The inferior borders of the lower ribs were eroded bilaterally. The Kahn test was negative. The patient was seen again two years later during which period he had led a normal life but had noted mild dyspnea and palpitation on exertion. At this time the chest film revealed an increase of the tumor to the dimensions of 10 by 8 cm. The preoperative diagnosis was aortic coarctation probably on the basis of a neurofibroma. Thoracotomy revealed a saccular aneurysm of the upper descending aorta, 11 cm. long and 8 cm. wide. Its attachment to the aorta was 7.5 cm. long. A smaller, daughter aneurysm arose from the large aneurysm. The aorta seemed constricted at its junction with the upper end of the aneurysm. Resection of the aneurysm and of the entire aneurysm bearing segment of the aorta was carried out. Reconstruction of the aorta was not done. During the postoperative period the blood pressure rose to 220/130. On the seventeenth postoperative day there was an episode of cardiac decompensation which responded well to treatment. About eight months after the operation the patient took up his regular activities. The chest film showed some symmetrical cardiac enlargement and an increase in the notching of the ribs. The blood pressure was 190/115. The urine was normal. Kidney function tests showed no abnormality.—*Aortectomy for Thoracic Aneurysm, J. Alexander & F. X. Byron, J. A. M. A., December 30, 1944, 126: 1139.*—(*H. Abeles*)

Mitral Stenosis and Silicosis.—The diagnosis of silicosis must be based on clinical evidence, not on roentgenological changes alone. In a 26 year old white man the roentgenological diagnosis of silicosis had been made. He had been working eighty-three days in a building in which a crusher of filter material was operated. The filter material consisted of finely ground silicate. The patient had far less exposure than 8 other persons who worked in the same building and of whom none developed signs or symptoms of silicosis. Physical examination of the patient revealed mitral stenosis. Fluoroscopy showed enlargement of the left auricle. Roentgenological examination revealed accentuation of the pulmonic conus and of the left auricular outline. There was diffuse mottling throughout both lungs, a picture similar to that found in silicosis. The pulmonary changes in this case were apparently due to congestion, resulting from mitral stenosis.—*Pulmonary Roentgenographic Changes Due to Mitral Stenosis Simulating Those Due to Silicosis, H. W. Ryder & H. G. Reineke, Am. Heart J., March, 1945, 29: 327.*—(*G. C. Leiner*)

Subacute Pulmonary Endarteritis.—Clinical cases in which *Streptococcus viridans* has produced isolated vegetations on the intima of the pulmonary artery are infrequent. It is not unusual, however, to have a spread from the pulmonary semilunar valves for some distance up the pulmonary artery. Isolated vegetations situated in the pulmonary artery above the valves are associated with pathological lesions of a varied nature, and of them congenital defects in the heart and great vessels are the most important. A case of *S. viridans* endarteritis is reported in a 4½ year old white girl. This patient died approximately eight weeks after the onset of the disease. The postmortem showed subacute bacterial pulmonary endarteritis with multiple septic infarcts in the right lung. No changes were found in the heart and great vessels which might account for the atypical localization of the vegetations. The vegeta-

tions in the pulmonary artery consisted, to a large extent, of necrotic tissue arising from the vessel wall. This is in accordance with the observations that the vegetations in endocarditis are derived largely from the tissue of the valves. In the present case, the lesions developed in the lesser circulation, involved an apparently previously healthy vessel wall, and occurred in an atypical location where undue mechanical stress could not be postulated. *S. viridans* localized, therefore, in a manner resembling that of the aggressive organisms encountered in acute endocarditis. This assumption also seems supported by the fairly rapid course of the disease. However, the appearance of the lesion and other important clinical and pathological findings are those usually found with subacute bacterial endocarditis. (With 2 plates.)—*Subacute Bacterial (Streptococcus Viridans) Pulmonary Endarteritis, A. E. Rhoden, Am. J. Path., May, 1945, 21: 507.*—(*J. S. Woolley*)

Exudative Pericarditis.—A new roentgenological sign of exudative pericarditis is described. It consists of a change of the heart shadow with respiration: The orthodiagraphic diameter of the heart decreases with inspiration and increases with expiration. A moderately large amount of pericardial effusion and a good respiratory motility of the diaphragm are necessary to produce this sign. It was seen in a 25 year old female in whom the clinical diagnosis of septicemia with pericarditis was made. The orthodiagraphic diameter of the heart was 15 cm. during the expirium and 12.5 cm. during the inspirium. At autopsy 300 cc. of fluid were found in the pericardium.—*Über Röntgensymptome bei exsudativer Perikarditis, L. Walldén, Upsala läkaref. förh., September 20, 1942, 48: 133.*—(*G. C. Leiner*)

Hemorrhagic Tuberculous Pericarditis.—Two cases of hemorrhagic pericarditis are described. Inoculation of the exudate into a guinea pig proved the diagnosis of tuberculosis. Both cases recovered, and the recovery is ascribed to the small number of the tubercle bacilli present and their mild virulence.—*Péricardites hémorrhagiques tuberculeuses curables, R. Dupérié, A. Fontan & R. de Lachaud, J. méd. Bordeaux, 1942, 119: 49.*—(*G. Simmons*)

Silicosis of Pericardium.—Silicosis of pericardium is rare. A 51-year-old white man, stonecutter, in whom a left pneumothorax had been induced for silicotuberculosis, was admitted to the hospital. On admission the chest roentgenogram showed a left hydropneumothorax with almost complete collapse of the lung, and diffuse nodular infiltrations throughout the right lung. Electrocardiographic examination revealed an inversion of the T wave and slurring of the QRS complex in lead II. The patient died with the signs of pulmonary insufficiency. On autopsy, silicotic foci and tuberculous cavities were found in both lungs. Silicotic foci were seen in the tracheobronchial and peribronchial lymph nodes. The heart weighed 360 g., the right ventricular wall measured 8 mm. in diameter, the left, 11 mm. The pericardial cavity was obliterated and the parietal pericardium was adherent to the left pleura. Microscopic examination showed silicotic foci within the visceral pericardium over the left ventricle. No silicotic foci were found in the myocardium. It is believed that these findings prove the communication between pleural and pericardial lymph vessels.—*Silicosis of the Pericardium: Case Report, Marguerite G. Stemmermann, Am. Heart J., May, 1945, 29: 642.*—(*G. C. Leiner*)

Erythema Nodosum.—The old view was that erythema nodosum is frequently, if not generally, an expression of rheumatism even when no other definitely rheumatic symptoms are present. More recently great doubt has been expressed regarding such specific association of the two conditions. The recognition of small epidemics of this condition led some observers to consider it a specific infectious disease. Isolation of a specific

causal organism, however, has never been confirmed. Studies revealed the fact that it is not infrequent for the eruption to be followed some months later by evidence of tuberculosis such as a pleural effusion or tuberculous meningitis. It has been shown in Scandinavia that the vast majority of children with erythema nodosum have strongly positive tuberculin reactions; in addition many cases present radiological evidence of enlargement of the hilar lymph nodes and, in a smaller number, shadows of primary tuberculosis. Several investigations have clearly shown that the occasional epidemics seen in schools and institutions are in the vast majority due to recent simultaneous infection with the tubercle bacillus. Very few of the attempts to demonstrate tubercle bacilli in the actual nodes have been successful and these few successes are probably explained by the assumption that the cultures were made at a time when there was a tuberculous bacillemia. As a result of these investigations the theory was put forward that erythema nodosum occurs during primary tuberculous infection at the time the patient first develops hypersensitivity to tuberculin. Punch (1941) observed that in a number of student nurses undergoing regular tuberculin-testing the change from a negative to a positive tuberculin reaction was marked by the development of erythema nodosum. However, in a series of 800 cases 5 per cent showed a negative tuberculin reaction. Furthermore cases of eruption have occurred in patients known to have been infected with tubercle years before and who show evidence of this old infection in the form of calcified hilar nodes. The occasional development of erythema nodosum after hemolytic streptococcal infections such as scarlet fever has been observed. Further, about 5 per cent of patients with coccidioidomycosis show typical erythema nodosum. Erythema nodosum is occasionally met with as an episode in the prolonged clinical histories of some cases of sarcoidosis. Occasionally, after the use of sulphonamides, an eruption indistinguishable clinically and histologically from erythema nodosum results—the eruption, however, fades away rapidly when the drug is stopped. In a series of 112 cases studied by the author, 38 were males and 74 females. Of these, 61 were strongly positive to 0.01 mg. of tuberculin. In 21 of the 61, the X-ray films showed enlarged hilar shadows and some of these also showed a shadow of the primary lesion. One patient had typical tuberculous cervical adenitis; one patient died later of tuberculous peritonitis and 4 cases subsequently developed a pleural effusion. Only 10 of the 112 cases had a history of acute rheumatism—in only 2 of these was there any evidence of a rheumatic relapse. The author concludes that erythema nodosum must be regarded as the result of a nonspecific reaction to a variety of infections or toxic agents and that it is not a specific disease.—*Aetiology of Erythema Nodosum, C. B. Perry, Brit. M. J., December 30, 1944, 2: 843.—(D. H. Cohen)*

Hodgkin's Disease.—A 44 year old, white man noted a lump on the midposterior aspect of the right calf in March, 1939. In August, 1939 it ulcerated and had a purulent discharge. Soon afterwards several more lumps developed in the surrounding region as well as on the opposite calf. A biopsy of the skin lesion was reported as idiopathic multiple hemorrhagic sarcoma. The patient received radiation therapy. In September, 1940 he first experienced chills, fever and sweating. He was admitted to a hospital in November, 1940. Physical examination revealed slightly enlarged submaxillary lymph nodes. The skin of the left buttock and of the right popliteal space showed multiple shallow ulcers. Many brown and grayish-black spots were present on both legs. There was a moderate secondary anemia. A blood culture was negative. A roentgenogram of the chest was essentially negative. Three days after admission the patient developed erythematous skin lesions which became nodular in character within twenty-four hours. Microscopic examination of the new lesions revealed a slight endothelial and fibroblastic proliferation about small blood vessels. The older lesions showed

findings typical of Hodgkin's disease. On the eighth hospital day hundreds of small papular nodular erythematous lesions appeared. Chills and fever were associated with the new eruption. The patient died eight days later. The autopsy diagnosis was Hodgkin's disease of the skin with metastases to the abdominal and pelvic lymph nodes, trachea, lungs, pleura, esophagus, stomach, liver, spleen and lumbar vertebrae. The occurrence of terminal blood-stream spread without any evidence of embolic cellular element dissemination is consistent with a virus etiology of Hodgkin's disease.—*An Unusual Case of Cutaneous Hodgkin's Disease with Terminal Blood Stream Spread, S. R. Bersack, J. A. M. A., December 16, 1944, 126: 1025.—(H. Abeles)*

Sarcoidosis.—Theories regarding etiology are reviewed and summarized in four categories: (*1*) nonvirulent tubercle bacillus, (*2*) a nonspecific tissue response to various organisms, (*3*) disease of the reticulo-endothelial system, similar to Hodgkin's disease, and (*4*) a chronic infectious granuloma possibly due to a virus. The pathological lesion resembles a miliary tubercle, being similar to the lesions Sabin has been able to produce in guinea pigs by injection of the phosphatide fraction of the tubercle bacillus. In all cases in which caseation was present, tubercle bacilli could be demonstrated, but none were demonstrable in the noncaseating lesion. The author does not rule out sarcoid because of the presence of a caseating lesion. The great majority of cases are hyposensitive or anergic to tuberculin. Clinical features include insidious onset and extreme chronicity. The manifestations depend on the structures involved, most commonly lymph nodes, lungs, skin, or bones. The disease is not incompatible with longevity. A case is presented which suggests kidney involvement because of nocturia several times nightly over a period of several years, pyuria, cylindruria and hypertension. Dyspnea led to X-ray examination which revealed bilateral hilar node involvement with bilateral productive infiltrations. Inguinal lymph node biopsy confirmed the diagnosis of Boeck's sarcoid. The patient is alive and able to carry on moderate work two years after diagnosis and three years following the original symptoms.—*Boeck's Sarcoid, W. L. Meyer, Dis. of Chest, November–December, 1944, 10: 509.—(K. R. Boucot)*

THE

AMERICAN REVIEW OF TUBERCULOSIS

ABSTRACTS

VOLUME LIII MAY, 1946 ABST. No. 4

World War I and Tuberculosis.—In the United States, World War I delayed the decline in tuberculosis mortality which had been going on for years previously. This mere failure of decline, however, meant that about 20,000 people more died yearly from the disease than would have died if the decline had not been arrested by the war. In most western Europen countries not only did the decline in tuberculosis mortality cease but there was an abrupt rise in deaths with each year of the duration of the war not only in belligerent nations but in neutral countries as well, that is, not only Belgium, England and France suffered from increases in tuberculosis mortality, but also the Netherlands and Denmark. Particularly severe was the sharp rise in mortality in Germany, Austria and Hungary. Thus in Austria the mortality rose from 259 in 1913 to 432 in 1917. In Russia and Poland the toll was even more appalling, for example, in the city of Lodz 1,164 per 100,000 died of the disease in 1917.—*World War I and Tuberculosis, G. J. Drolet, Am. J. Pub. Health, July, 1945, 35: 689.*—*(M. B. Lurie)*

Tuberculosis Control in Venezuela.—The population of Venezuela is 4,000,000. The greater part of the country is almost uninhabitable. Therefore, the population is concentrated along the Carribean coast to the north and the range of the Andes to the West. The average general population density is 7 inhabitants per square mile. Present knowledge of the tuberculosis problem is based on surveys undertaken since 1936. These cover 250,000 observations by tuberculin testing and chest X-raying. In urban centres mortality reaches an average of 250 per 100,000, fluctuating from 210 to 470. Tuberculosis reaches 12 to 23 per cent of the general mortality in certain cites. Caracas has shown some decline in mortality from 600 to 700 in 1900 to 241 in 1943. Morbidity in urban centres is 2.43 per cent, in rural areas 1.02 per cent, and among the Indians 0.98 per cent. Tuberculin testing reveals 20 per cent reactors in children under 4 rising to 83 per cent in those above age 14 living in urban centres. Adults in semirural centres are 25.9 per cent tuberculin-positive, in rural centres 27.3 per cent, and among the Indians 25.9 per cent. Venezuela's antituberculosis campaign began in 1936 with the creation of a Tuberculosis Division within the Ministry of Public Health and Social Welfare. This Division controls dispensaries and sanatoria and defines standards to be followed by private agencies. The sanatorium "Simon Bolivar" in Caracas has been organized as the National Tuberculosis Institute. Twenty-one dispensaries cover the most important cities. They carry on epidemiological studies, ambulatory collapse therapy, act as the sole agencies for referring patients to sanatoria and supervise the work of the Tuberculosis Associations. A sanitary regulation requires all workers to present a health certificate. This greatly increases case-finding activities. Shortage of nurses greatly handicaps the whole structure of the tuberculosis control movement. In Caracas 4 contacts per case have been examined during the past year. The prevalence of active disease is 7 per cent in contacts. For rural areas travel-

ing clinics with X-ray equipment proved a failure; therefore public health doctors are now being trained to head Public Health Units acting as secondary networks of tuberculosis clinics to care for the 66 per cent population in rural areas. There are 1,200 beds now available for tuberculous patients; 450 beds are being added. Tuberculosis Associations are especially engaged in seeking more beds and developing an educational program. In 1937 the Venezuelan Phthisiological Society was founded. It acts as Advisory Board of the Division of Tuberculosis.—*The Tuberculosis Problem and the Organization of the Tuberculosis Campaign in Venezuela, J. I. Baldo, Dis. of Chest, May-June, 1945, 11: 259.*—*(K. R. Boucot)*

Tuberculin and X-ray Studies in Twins.—Four hundred forty pairs of twins, of which 146 (33.1 per cent) are considered as monozygotic and 294 (66.8 per cent) as dizygotic, were studied. If the patch test of Vollmer was negative the intracutaneous test with 1 mg. of Old Tuberculin was done. X-ray studies were made at the same time. The age of the twins varied from 6 to 15 years with an average of 9.6 years. Among the 880 twins, 243 (27.6 per cent) were tuberculin-positive and 637 (72.3 per cent) tuberculin-negative. The proportion of the twins with allergy was exactly the same between the identical and nonidentical twins. In 61 (13.8 per cent) pairs both twins had a positive reaction, in 258 (58.6 per cent) both had a negative reaction. In 121 (27.5 per cent) pairs one twin was positive and the other twin negative. This allows the conclusion that in a majority the infection was not contracted simultaneously. Of the twins 81.3 per cent went to the same school and 18.6 per cent to different schools. There was no difference in tuberculin tests if the twins did not go to the same school. The index of 27.5 per cent of positive results in the twins proves to be inferior to the results obtained in other groups of school children in Argentina, which were between 29.5 per cent and 41.1 per cent in different groups of children with an average age from 8.5 to 9.2 years. The genotypic factor does not exert any influence on the acquisition of tuberculous infection. Twenty and four-tenths per cent of the twins between 6 and 7 years had a positive reaction. The percentage of positive reactions was found highest in the group between 12 and 15 years where it was 49.3 per cent. X-ray study showed the existence of pulmonary lesions in 33 twins which were part of 22 pairs, 10 monozygotic and 12 dizygotic. In 11 pairs (4 identical and 7 nonidentical) both twins had X-ray evidence of pulmonary involvement. In the 11 other pairs, 6 identical and 5 nonidentical, only one of the twins was affected. Neither increase in the hilar markings nor increase of the bronchovascular markings was considered as pathological. Thirty-two cases showed some evidence of pulmonary lesions of tuberculous origin, one had hydatid cyst of the lung. Of those 33, 23 (69.6 per cent) had also a positive skin reaction. The remaining 10 cases (30.3 per cent) had a negative skin reaction. Of the 22 pairs in which both twins had X-ray evidence of tuberculosis, all lived in the same medium but 10 went to different schools.—*Examen radiologico-tuberculinico de 440 paresade gemelos en edad escolar, R. F. Vaccarezza, J. Dutrey & E. M. Olivieri, Prensa méd. argent., August 24, 1945, 32: 1659.*—*(W. Swienty)*

Tuberculin Reaction and Environment.—It has been possible for several years to complete tuberculin testing of school children in several Norwegian cities. Tuberculosis in school children is generally characterized by primary infections and runs a benign course; therefore, an examination so limited is of little significance in combating infection. However, when the work was extended to include environment investigations centering about the tuberculin reactors, it then became valuable and the prospects of discovering sources of infection increased. This author carried out such an investigation in Bergen, Norway; 12,000 school children were examined. All reactors were subjected to photofluoroscopy and all the Pirquet negative scholars were advised to undergo BCG vaccination. Of those

tested in all grades, 1,236 were found to be Pirquet positive and 1,155 of this group were screen-photographed. Three cases of active pulmonary tuberculosis were found, 11 cases of hilar adenitis and one case of pleuritis. Environmental investigation disclosed that more than one-half of those found to be positive were already known to the Public Health Service, but 6 new cases of infectious tuberculosis were discovered. The author has recommended the environmental investigations of tuberculin-reacting school children as an important aid in the campaign against tuberculosis.—*Tuberculin and Environment Investigation of School Children, E. Berle, Acta. med. Scandinav., October 19, 1943, 115: 219.*—(*E. R. Loftus*)

Tuberculin Reaction.—A number of patients with Ghon tubercles and calcified hilar nodes had negative tuberculin reactions. Since positive reactions are believed to indicate sensitivity produced by living tubercle bacilli in the tissues, it would seem that, if the tuberculin reaction became negative during repeated tests, this would indicate that living bacteria no longer existed in the tissues or were so completely walled off that there was no antigen available to induce the formation of antibodies. Also, since an increasing number of individuals receive only minimal infection with tubercle bacilli and are completely desensitized when the tubercle bacilli die off, such infections may be missed in the usual tuberculin testing of a community. One hundred and twelve children with Ghon complexes were studied at the Mayo Clinic. The age range was from 3 to 15 years. The largest group consisted of 12 and 13 year olds. There were 56.3 per cent males. Under age 12 there were more reactors than nonreactors. Between ages 12 and 15, there were more nonreactors than reactors. Of 20 with a history of exposure to tuberculosis, 15, or 75 per cent, reacted to the first strength of PPD. In 7 patients with tuberculous lesions in addition to their Ghon lesions, all were positive to the first strength. The geographical distribution corresponded to that of all Mayo Clinic patients. Therefore, patients with calcified lesions were not restricted to a particular area. Fifty-seven, or 50.9 per cent, of the 112 children were positive to the first strength of PPD. Such deviation from the anticipated 100 per cent cannot be accounted for on the basis of random sampling. Twenty-three of the 55 nonreactors to the first dilution were given a second test (0.005 mg. PPD per 0.1 cc.). Eleven, or 47.8 per cent, were positive to this second dilution. Bernard *et al.*, in studying 184 patients ranging in age from 12 to 15 years who had positive X-ray evidence of tuberculosis, found only 7 1 per cent failed to react to 1 mg. of OT. Wells and Smith found 55 per cent of 128 negative. Gass *et al.* found little association between the tuberculin reaction and calcified lesions in 573 cases. Lloyd and MacPherson found that of 203 healthy normal children with positive tuberculin reactions, 2 per cent changed to negative after a two-year interval. Aronson and Dannenberg, after a five-year interval, found that 9 per cent of 86 patients shifted to negative from positive. Therefore, loss of sensitivity is not infrequent, but is no indication of waning immunity according to Willis and Sewall *et al.* A negative reaction to tuberculin in humans is no evidence that the individual never was infected nor that acquired resistance is lacking as stated by Rich. With an increase in minimal tuberculous infection and complete healing of primary tuberculosis, an individual may fail to react to tuberculin. This seems possible in view of the findings of Feldman and Helmholz that Ghon tubercles from a child 20 months old were negative for tubercle bacilli when a suspension of the tubercles was injected into guinea pigs. Whether such persons may again respond to tuberculous infection with a primary complex as apparently occurred in some of the cases presented by Terplan must be determined by the study of a larger series.—*Tuberculin Reaction in Children with a Ghon Complex: Review of 112 Cases, Mildred A. Norval, Am. J. Dis. Child., July, 1945, 70: 1.*—(*K. R. Boucot*)

Pulmonary Zones.—This study is based on examination of 188 humans and 90 other mam-

mals. The classic concept of pulmonary asymmetry with three right and two left lobes is inexact. In 50 per cent only two lobes were found on the right, and in 15 per cent there were three lobes on the left. Moreover, fissures were found only in pathological states or other special circumstances. The theory that the right upper lobe is superadded is incorrect, for embryological study shows that the right upper and middle lobes are homologues of the left upper and middle zones. These latter zones are found joined together in 85 per cent of the cases, with only a thin interzonal partition. Nine zones are found in each lung, each autonomous from the standpoint of bronchovascular, lymphatic and nerve supply. The zones are separated by two thin interzonal elastic membranes, homologues of the fissures, or by a fissure and a membrane. The right upper, middle, and lower lobes have three, two, and four zones, respectively, while the left upper and lower lobes have four and five. The existence of these zones, pyramidal in shape, with apex towards the hilum, is confirmed by dissection, injection of radio-opaque material in pathological specimens, and clinical and radiologic studies in tuberculosis, pneumonia, carcinoma of the lung and lung abscess.—*Zones pulmonaires et zonites: Anatomo-radiologie des zonites partielles ventrales moyennes droites, P. Coulouma, Schweiz. med. Wchnschr., August 19, 1944, 74: 886.*—(*J. Gerstein*)

Soil and Primary Infection.—A report is given of 4 simultaneous cases of erythema nodosum in a family with 6 children, whose mother was an undiagnosed open case of pulmonary tuberculosis. All children were in poor general condition due to bad economic circumstances. Five of them showed evidence of active primary infection with unusually pronounced pulmonary and glandular involvement. Only one child remained free from tuberculosis and had a negative skin test. These observations are interpreted as a proof of the importance of the soil in tuberculosis. The similarity in the above cases in the form and development of the primary infection with a particular tendency to skin manifestations, such as erythema nodosum, is attributed to a special familial sensitivity towards the tubercle bacillus.—*Terrain et primo-infection (a propos de quatre cas d'érythème noueux familial simultanés, J. Genévrier & Fr. Bordet, Rev. de la tuberc., January-February, 1941, 6: 84.*—(*V. Leites*)

Exogenous Reinfection in Tuberculosis.—The theory of endogenous reinfection and the supporting arguments are submitted to a critical reevaluation. The question is brought up why single or repeated exogenous reinfections could not produce the same effect as bacilli derived from the primary complex and whether it is admissible to attribute more aggressive properties to the tubercle bacilli originating from an endogenous source. The theory that primary infection confers a specific life-long resistance against exogenous reinfection is not well founded. A relative resistance against exogenous reinfection has been experimentally demonstrated only against a certain quantity of bacilli and only in certain animals which had been recently and massively infected. This does not necessarily apply to human primary infection. Reference is made to the studies carried out in collaboration with Saenz and Canetti demonstrating sterilization of primary foci and even disappearance of tuberculin sensitivity after primary infection. The clinical argument in favor of endogenous reinfection, implying that exposed adults do not present a higher morbidity than nonexposed ones, is considered erroneous, as proved by statistical data (Rist, Simon, Opie, McPhedran). The argument of the practical non-existence of marital tuberculosis is without foundation, since it has been found in 25 to 30 per cent of cases. However, marital tuberculosis rarely occurs simultaneously, which explains the fact that its frequency was not noticed by some observers. For all these reasons exogenous tuberculosis is considered not only possible but even rather frequent. The possibility of endogenous origin of tuberculosis cannot be denied, but it represents a pathogenic mechanism which is neither ex-

clusive nor very frequent.—*Reinfections exogènes dans la tuberculose, P. Ameuille, Rev. de la tuberc., 1939–40, 5: 1370.*—(*V. Leites*)

Reinfection Lesions.—In 100 autopsies of subjects who had died of nontuberculous diseases around the age of 45, 64 were found to have latent tuberculous reinfection lesions. The endogenous or exogenous origin of these lesions is discussed. There is no macroscopic nor microscopic criterium which would permit to decide this question, but one can investigate whether at the time of reinfection the primary complex still contained living tubercle bacilli which would make an endogenous reinfection possible. The virulence of the primary complex is neither indefinite nor extremely long lasting as formerly believed. Inoculations of primary complexes revealed that these lesions are sterile in 50 per cent at the stage of caseation and in 80 per cent at the stage of calcification and fibrosis. According to these findings, primary complexes would contain virulent bacilli only in about 20 per cent a few years after primary infection, that is, during childhood, adolescence and early adulthood. The opinion is expressed that most reinfection lesions occur at a later age. Some develop in childhood consecutively to postprimary dissemination, resulting in Simon foci, but they are considered very rare. On the other hand, statistics are quoted indicating an increase in reinfection lesions between the ages of 30 and 60. These two facts, early sterilization of the primary complex and relatively late occurrence of reinfection lesions, indicate that the majority of reinfections must be of exogenous origin. From a pathological viewpoint, the main difference between primary and latent reinfection lesions is the absence of lymph node participation in the latter, the pathological aspects of the lesions themselves being rather similar. The possible causes for this change in lymph node reaction are: (*1*) difference in the age at which primary and reinfection lesions occur, the participation of lymphatic tissue being always more important in childhood; (*2*) the nonspecific alterations produced in the course of time by nontuberculous causes in the lymph nodes (anthracosis, silicosis); (*3*) a state of allergy produced under the influence of a preceding primary infection. —*Le diagnostic anatomique des lésions de réinfection latente, G. Canetti, Rev. de la tuberc., 1939–40, 5: 1391.*—(*V. Leites*)

Bacteriology of Tuberculous Cavities.—Thirty-three postmortem examinations were made on the bacteriologic flora associated with tuberculous pulmonary cavitation. Staphylococci, streptococci, pneumococci and micrococcus catarrhalis were found in the exudate of cavities and their draining bronchi in the frequency named. Within the walls of the cavities only tubercle bacilli were demonstrable. In no instance were other organisms found within the walls in intimate association with tubercle bacilli. The authors conclude that tuberculous pulmonary tissue is refractory to pyogenic infection.—*La flora microbiana de las cavernas tuberculosas pulmonares, A. A. Raimondi, R. Scartascini & F. M. Gonzalez, Arch. argent. de tisiol., October–December, 1944, 20: 367.*—(*R. Kegel*)

Prognosis in Tuberculosis.—Study of the sedimentation rate and of the sputum for tubercle bacilli was found to be helpful in predicting the prognosis of patients with tuberculosis. The material comprises 2,500 cases, and the observation period was from five to fifteen years. The sedimentation rate at the beginning of the period of observation, or when the patient's sputum was first found to be positive, is a very valuable prognostic sign. At the end of ten years, 33 per cent of patients with normal sedimentation rates were dead, whereas 75 per cent of patients with high sedimentation rates had died of tuberculosis. Of even greater importance was the value of the sedimentation rate at the end of the first period of sanatorium treatment, which was at least three months in each case. It was found that at the end of ten years 25 per cent of those discharged with normal sedimentation rates were dead, whereas 80 per cent of those discharged with elevated sedimentation rates had died. The importance of the bacteriological

findings in the sputum is appreciated when it is noted that among those discharged with a negative sputum 30 per cent were dead within ten years, whereas 73 per cent of those with positive sputum were dead at the end of the same period of time. Although a favorable prognosis can be given to a patient who is discharged with a negative sputum and a normal sedimentation rate, it is to be noted that the death rate among this favorable group is still three to four times higher than that of the corresponding normal death rate. It is also noteworthy that this favorable group comprises only about 10 per cent of those discharged alive.—*The Influence of the Sedimentation Rate and the Bacteriological Finding during the First Period of Care on the Prognosis in Cases of Open Pulmonary Tuberculosis, G. Berg, Acta med. Scandinav., June 23, 1942, 110: 558.—(H. Marcus)*

Incipient Pulmonary Tuberculosis.—The authors have studied 300,000 X-ray plates and have found among them 68 cases of incipient tuberculosis. The interval between normal and first pathological findings as evidenced by X-ray examination was generally one year, in some instances longer, but always less than two years. Among the 68 detected cases of incipient tuberculosis, 42 had an interval between a normal and a pathologic X-ray film of less than one year, and 26 of one to less than two years. The cases are divided into primary and postprimary infections. The authors prefer the expression "postprimary" to "reinfection." There were 9 primary infections of which 6 showed parenchymal, 2 pleural localization. One case had a possibly true primary bronchial lesion. The primary infection was exclusively in subjects 14 to 21 years of age. Only 2 were 23 and 24 years of age, respectively. The detection of the disease was so early that no spread had occurred. There was swelling of the mediastinal lymph nodes in all cases, but the reaction of the nodes was less than in children. All were found by routine X-ray examination but for one case who had an erythema nodosum. The tuberculin reaction did not give any indication as to the severity and development of the pulmonary lesions. In 2 cases tubercle bacilli were found. Fifty-nine cases of postprimary infection were found. Fifty-eight cases had incipient pulmonary lesions. One case was an incipient bronchial tuberculosis, which is thought to be postprimary. This shows the enormous preponderance of the localization of the reinfection in the pulmonary parenchyma. As to the localization, 60 cases (91 per cent) were unilateral. The right lung was infected in 36 cases and the left in 24 cases. Six (9 per cent) showed bilateral localization, but 5 of the latter had an X-ray film taken at an interval longer than one year, so it is possible that they had really begun as unilateral cases but escaped detection. Thirteen per cent of the unilateral cases showed cavitation. The type of disease was infiltrative in 44 (68.75 per cent), nodular in 12 (18.75 per cent), infiltrative-nodular in 8 cases (12.50 per cent). Tracheobronchial lesions without X-ray evidence but with positive bronchoscopic findings were present in 2 cases. Most of the infiltrates were localized in the lateral subclavicular region; so were most of the nodules. The infiltrative-nodular type was localized with equal frequency in the apex, in the lateral and medial subclavicular regions. The postprimary tuberculosis or reinfection was diagnosed only if tuberculin allergy existed in subjects who were negative from a clinical and X-ray standpoint. Almost all had been contact cases. There was X-ray evidence of calcification or other signs of healed primary infection with complete absence of adenopathy. The postprimary infection is either localized in previously normal lung tissue or is a reactivation of a previous childhood infection. Ten per cent were reactivations of previously existing foci. The bilateral cases are generally localized in the apices and correspond to reactivation of previously existing foci. An important portion of the unilateral cases are evidently due to coalescence of several preëxisting foci at the site of a perifocal exudate. There was no case of hematogenous or of bronchial spread. The sputum contained tubercle bacilli in 76.66 per cent of 30 cases in which bacteri-

ological studies were made. Hemoptysis was one of the early symptoms and was present in 7 cases. The most common age was between 21 and 30 years (29 cases); 23 cases were between 15 and 20 years. The infiltrate was most frequent in the age group between 21 and 30 years. There was no difference in sex distribution. An important portion of the early infiltrates seem to be of exogenous origin by contact and favored by a depression of specific and nonspecific defense reactions of the organism. Eight cases showed the first symptoms of tuberculosis during or after pregnancy; of these, 2 during the first three months, 2 in the eighth month of pregnancy and 4 during the first two months of the puerperium. Not included in these findings are numerous cases of purely pleural beginning of tuberculosis in pregnant women. In only 7 cases could an exogenous superinfection be proved; all were in hospital personnel; 2 were physicians and 5 were nurses. All of them had a high allergic reaction previous to the beginning of their pulmonary disease. Six showed infiltrates, one an early cavitation and the remaining case was of the infiltrative-nodular type. The localization was in the right lung in 6 cases.—*Formas de iniciacion de la tuberculosis pulmonar del adulto, A. C. Artagaveytia, L. E. Matos, C. S. Laso & A. Crisci, Rev. de tuberc. d. Uruguay, March 12, 1944, 12: 287.*—(*W. Swienty*)

Incipient Pulmonary Tuberculosis.—This is a study on 35 cases of initial lesions observed at a tuberculosis clinic for pre- and postnatal and student prophylaxis. The interval between normal X-ray findings and the appearance of the lesions was less than three months in 9 cases, less than six months in 14, less than nine months in 21, less than twelve months in 25, less than fifteen months in 30, and less than eighteen months in 35 cases. In 4 cases the appearance of the lesions coincided with the turning positive of the tuberculin reaction: in these cases the possibility of a primary tuberculosis can be admitted. Eighty-eight and four-tenths per cent of the cases showed positive tuberculin reactions previous to the appearance of the lesions. Most of these patients were asymptomatic until the X-ray diagnosis was made, except cases with pleural involvement and with acute caseous disease. The symptoms, when present, were: hemoptysis, grippal syndromes, persistent upper respiratory infections, erythema nodosum and in one case a typhoid status. Pulmonary infiltrates with or without cavitation constituted 48.6 per cent of the cases. The remainder of the cases were: corticopleuritis with effusion, tracheobronchial lymphadenopathy, caseous bronchopneumonia, nodular hematogenous tuberculosis and bronchial tuberculosis. It was noteworthy that tuberculous pleurisy and corticopleuritis was twice as frequent in pregnant women as in the other patients. In 29.40 per cent of the cases there was cavitation present at the moment of X-ray diagnosis. Only 28 per cent of the cases showed roentgenological changes previous to the appearance of the active lesions.—*Formas de iniciación de la tuberculosis pulmonár en el adulto, F. D. Gomez & C. Epifanio, Hoja tisiol., June, 1945, 5: 2.*—(*L. Molnar*)

Interstitial Tuberculosis.—A special form of pulmonary tuberculosis is described, which is thought to be clearly distinct from common bronchogenic phthisis as well as from disseminated tuberculosis. The radiological characteristics are: (*1*) trabecular and reticular changes forming a network which is wider near the hilum and denser at the periphery, suggesting lobular contours; (*2*) micronodular infiltrations, miliary or submiliary in size. These two elements are combined in various ways resulting in different radiological aspects. The lesions are mostly bilateral, although predominantly unilateral cases may occur. Another characteristic feature is the mainly cortical localization of the infiltrations. Two categories of cases are recognized: (*1*) the pure reticulo-nodular forms; (*2*) reticulo-nodular forms accompanied in the course of their development by infiltrations and cavity formations of various extent. The lack of important clinical symptoms in association with the extensive X-ray findings is characteristic.

The patients are in good general condition and are mostly afebrile. Another diagnostic feature of these forms is the frequent association with pleural and laryngeal involvement, the former being present in two-thirds of cases. Laryngeal complications were found in approximately 30 per cent of cases (as compared to 10 per cent in bronchogenic tuberculosis). The laryngeal lesions were nodular or ulcerative in character. The majority of these patients had very slight expectoration. Some had negative sputum or sputum containing a relatively small number of bacilli. These facts made a direct propagation of bacilli from the lung to the larynx unlikely. The propagation is thought to be lymphogenous (in the submucous lymph system). The development of these forms of pulmonary tuberculosis is extremely variable, ranging from complete radiological clearing to extensive fibrosis. The third possibility is the formation of new infiltrations which can go on to absorption or excavation. The formåtion of new lesions is clinically almost always silent in these forms of tuberculosis. The anatomical basis of the described syndrome is thought to be an involvement of the interstitial tissue of the lymphatics and perilobular spaces combined with miliary tubercles, located as well in the interstitium as in the alveoles. The progression is felt to be lymphogenous (within the lung itself and to distant organs).—*Syndrome radio-clinique commun a certaines formes de tuberculose pulmonaire d'allure interstitielle prédominante, F. Tobé, M. Degeorges & J. Chenebault, Rev. de la tuberc., July–October, 1941, 6: 377.*—(*V. Leites*)

Oto-cardiac and Oculo-cardiac Reflexes in Pulmonary Tuberculosis.—On female patients suffering from pulmonary tuberculosis it is of great importance to study the autonomic nervous system, whichever be the parasympathetic imbalance present. This study is of value only when done together with X-ray studies and other tests since alone they are of little help in the evaluation of the progress of the disease. Several tests exist for the examination of the autonomic nervous system. The oto-cardiac and oculo-cardiac reflexes were studied; 64 female patients were examined. The following conclusions are drawn: (*a*) The oculo-cardiac reflex is a better index for the evaluation of the progress of the disease than the oto-cardiac reflex. (*b*) Often both reflexes are not in accordance with other tests, usually performed, as far as the prognosis of the disease is concerned. (*c*) In 97 per cent of the cases studied both reflexes were reversed. (*d*) These reflexes should be looked for routinely in order to formulate a more accurate prognosis. (*e*) The instability of the reflexes is related to the instability of the autonomic nervous system and to tuberculosis. The authors refer to Balaize who studied 100 patients and drew the following conclusions: (*1*) The number of increased reflexes is less than normal in tuberculous patients, while the number of reversals is higher. (*2*) Prognosis is good on patients with an exaggerated oculo-cardiac reflex (somewhat vagotonic). (*3*) Prognosis is bad on patients with a sympathicotonic reflex. (*4*) The evolution of the reflex parallels the favorable prognosis of the disease. (*5*) Reversal of the reflex or a noticeable decrease in the pulse rate follows aggravation of the disease.—*Reflejo oculo-cardiaco y oto-cardiaco in la tuberculois pulmonar, A. P. Heudtlass, J. A. Marti & A. Adamo, Bol. d. Hosp. F. Santojanni, 1945, 1: 175.*—(*P. B. Franca*)

Treatment of Hemoptysis.—Ten cc. of novocaine, 1 per cent, were injected into the stellate ganglion according to White's technique in 3 cases of severe pulmonary hemorrhage. If the site of injection is correctly chosen, a Claude-Bernard-Horner's syndrome becomes manifest and persists for about thirty minutes. In each of the 3 patients thus treated the hemorrhage stopped and the injections were repeated at four-day intervals to prevent recurrence or to stop hemorrhages if they recurred.—*Trois cas d'hémoptysie traité aves succes par infiltrations anesthétique du ganglion sympatique cervical stellaire, F. A. Toury & J. Vicaire, Rev. de la tuberc., 1941, No. 9/10, 6: 571.*—(*G. Simmons*)

Early Diagnosis of Tuberculosis.—From 1924 through 1939 there was a steady decline in the annual number of cases of respiratory tuberculosis in up-state New York. Beginning in 1940 in males there was a striking increase in cases reported. A less marked increase occurred in females in 1942. The increase in reported cases in males was largely due to an increase in minimal cases in the age group 20 to 34. In females, the increase was largely due to an increase in minimal cases in the age group over 35. It is believed that the increase in reported cases was not due to a greater development of tuberculosis during this period but to the discovery of more cases by the mass chest X-ray examinations practiced by the army and industrial institutions during this time. An upward trend in the proportion of minimal cases reported began before the increase in the total number of cases reported, suggesting an improvement in the early diagnosis of the disease which was independent of the mass X-ray surveys. Respiratory tuberculosis is now primarily a disease of adults in both sexes during the period of greatest social and economic significance.—*Recent Trends in the Early Diagnosis of Tuberculosis, E. X. Mikol & R. E. Plunkett, Am. J. Pub. Health, December, 1945, 35: 1260.—(M. B. Lurie)*

Roentgenology of Regional Anatomy of Lung.—This is a long, well illustrated article not fit for abstracting. It should be read in the original since without illustrations it is difficult to follow. The following summary is offered: *(1)* The X-ray topography of the postero-anterior region of the antero-superior lobules is studied. This is called supra-hilum posterior region. *(2)* The supra-hilum posterior region rests on a practically immovable surface and its slight movements are indirectly caused by the diaphragm and the ribs when these act upon the whole bronchial tree, pushing the main bronchus downward, outward and forward. *(3)* In the supra-hilum posterior region the greatest percentage of tertiary cavities are localized. *(4)* It is in the supra-hilum posterior region where most of the residual hematogenous lesions of primary infection are localized. *(5)* The radiological study of this region is of interest especially in cases of subclavicular, supracisural, hilar-apical and hilar-clavicular infiltrations.—*Topografia radiografica de regiones especiales del pulmon, S. P. Heudtlass & J. Marti, Bol. d. Hosp. F. Santojanni, 1945, 1: 39.—(P. B. Franca)*

Fluoroscopy of Diaphragm.—Determination of pleural lesions is of the utmost importance in predicting the success of pneumothorax in pulmonary tuberculosis. After observing 600 patients over a period of four weeks it was found that ordinary anterior-posterior fluoroscopy was not sufficient for examination of the costophrenic sinus. In 171 of the 600, pleural changes were evident. In 55.8 per cent changes were present in the anterior part of the sinus, in 7.6 per cent in the anterior and posterior, in 15.6 per cent in both, and in 21.0 per cent throughout. Only in the latter group could antero-posterior views show abnormalities. This emphasizes the need for turning patients in all directions in examining the costophrenic sinus.—*Beitrag zur Durchleuchtungstechnik des Zwerchfells, H. C. Iselin, Schweiz. med. Wchnschr., July 28, 1945, 75: 659.—(J. Gerstein)*

Azygos Vein.—Roentgenographically the azygos vein can be demonstrated in about 25 per cent of all antero-posterior views as a small knob-like shadow in the right tracheobronchial angle. It may be confused with a lymph node in this position. Slight turning of the patient may bring the shadow into view in a greater number of cases. The part of the vein that is visible is the horizontal curve as the vein bends over the lung root to join the superior vena cava. When an azygos "lobe" is present the vein swings out laterally and in its course over the lung it squeezes off a portion. This is not a true accessory lobe because it is only incompletely separated from the right upper lobe and has no true bronchus or blood supply of its own. Since the vein is extrapleural, the azygos pseudolobe is sepa-

rated from the right upper lobe by both the parietal and the visceral pleura, four layers in all. This explains why the azygos "lobe" frequently fails to collapse when right pneumothorax is induced. In such cases it is easily seen suspended, as it were, from the dome of the pleura, and it has been mistaken for broad adhesions.—*Die Vena Azygos im Roentgenbilde, H. Schenk, Schweiz. med. Wchnschr., June 9, 1945, 75: 522.*—(*H. Marcus*)

Photofluorography and Fluoroscopy.—The problem discussed is the examination of as large a segment of the population as possible in order to eradicate tuberculosis. The method suggested is costly and involves much work, but is quicker than any other. Fluoroscopy and photofluorography are to be used together, with the former done first. Films may then be taken in special positions. The disadvantages of the photofluorograph when used alone, including hiding of large areas of the lungs by heart and diaphragm, confusion of muscle and breast shadows, and difficulty in examining apices, are eliminated by fluoroscopy. The following administrative and nontechnical problems are then discussed; education of the population in the problem of tuberculosis; education and choosing of physicians for the job; examination of units like schools and factories first; preparation of equipment needed for the job; examination of contacts at frequent intervals; social help for the tuberculous.—*Die Reihendurchleuchtung und das Schirmbildverfahren, M. Hopf, Schweiz. med. Wchnschr., December 30, 1944, 74: 1356.*—(*J. Gerstein*)

Photofluorography.—The principle of the photofluorograph was first described by Bleyer in 1896, but was not developed further until 1921, when Schinz described the process and improved upon it. The present study began in 1939 when X-ray films were taken on 5,762 students, workers and army personnel. The advantages of speed and cheapness made screening of large numbers easy. Technical improvements were so great that there were only 33 failures for such reasons. The 24 by 24 mm. film was found to be the best, but the 68 by 68 mm. film was better for detail in miliary tuberculosis and silicosis. One of the special problems is ability to read the film, as shown by large variation in positive findings with different examiners. A special key for the description of positive findings is given. Using this, the investigators found that 84 per cent were normal, 6 per cent had insignificant and 10 per cent had significant pathological changes. Less than one per cent of the total had tuberculosis.—*Zweck, Organisation, Durchführung und vorläufige Ergebnisse der Schirmbilduntersuchung, H. R. Schinz, Schweiz. med. Wchnschr., August 19, 1944, 74: 879.*—(*J. Gerstein*)

Morgan Timer.—Examination of large population groups by photofluorography poses special problems because of the rapidity at which the procedure is conducted, the difficulty of obtaining retakes, and the need for uniformity in technique in order that interpretations be accurate. A photo-electric timing mechanism has been developed to control automatically the photofluorographic exposure. This eliminates the need for measuring individuals or adjusting the roentgenological equipment. The phototimer consists primarily of a multiplier phototube and a condenser-thyratron-relay system. Since the response of the phototube is directly proportional to the illumination of the fluorescent screen, exposure times will be long when the brightness of the screen is low in thick-chested individuals, and short when the fluorescent screen is bright in thin-chested individuals. A daily adjustment of kilovoltage and milliamperage settings to convenient positions is made. Thereafter, after placing the subject before the photofluorographic hood, all that is necessary is to close the exposure switch. Because different interpreters prefer different levels of radiographic density, the phototimer is equipped with a sensitivity control so that density may be regulated.—*Automatic Exposure Control in Photofluorography, R. H. Morgan, Dis. of Chest, March—April, 1945, 11: 150.*—(*K. R. Boucot*)

Fatal Intrapleural Injection of Lipiodol.—Following the intrapleural injection of lipiodol in a patient with a chronic bronchopleural fistula, the patient started coughing violently; there was malaise, later on dyspnea and cyanosis. The patient died five days later. It is assumed that the cough caused the lipiodol to be dispersed in fine drops throughout the lungs causing reflex constriction of alveoli and changes in the capillary permeability which led to acute pulmonary edema and fatal asphyxia.—*A propos des injections intrapleurales en cas de fistule bronchopleurale. Une complication mortelle, J. Rolland, Rev. de la tuberc., 1943, No. 4/6, 8: 91.*—(*G. Simmons*)

Thorium Oxide for Demonstration of Cavities.—A 25 per cent colloidal solution of thorium oxide is very fluid and flocculates when it comes in contact with tissues. It was used for the visualization of tuberculous cavities and results obtained were better than those given by lipiodol. Ten to 40 cc. were injected transthoracically and no untoward effects were encountered. The outline of the cavity is well visualized; multiloculated cavities and intercavitary septa can be recognized as such and the draining bronchus can be seen. No general reactions occurred. Thorium oxide was also used intrapleurally and for the diagnosis of bronchopleural fistulae. For the diagnosis of bronchial lesions, however, lipiodol is preferred.—*Emploi de l'oxyde de thorium pour l'opacification des cavités pulmonaires, Ch. Gernez-Rieux, Garcenot & Morseau, Rev. de la tuberc., 1944, No. 1/3, 9: 9.*—(*G. Simmons*)

Fluorescent Microscopy.—To determine the value of this method as compared with the Ziehl-Neelsen stain many smears were made in duplicate of sputum, gastric contents, urine, pleural fluids, etc. One set was stained by immersion in a staining bath using a modified Ziehl-Neelsen technique and the other was stained with 0.1 per cent auramine for fluorescent examination. Specimens in the latter group were fixed to the slide with egg albumen, which in itself is faintly fluorescent. This characteristic, however, aided in focusing and thus eliminated the objectional feature of having to work with a totally black field when only an occasional bacillus was present. The fluorescent method gave definitely more positives than the Ziehl technique, especially with pleural fluids, which showed nearly twice as many positives by fluorescence as with the other method. The overall results, however, were closer. Of 2,918 specimens, 50.5 per cent were positive microscopically when stained according to Ziehl-Neelsen, whereas 60.6 per cent were positive on fluorescent examination. Some doubt was expressed as to the specificity of some of the fluorescent positives in view of the clinical and roentgenological findings. This inspired studies in which specimens from fluorescent-positive Ziehl-Neelsen-negative cases were inoculated into guinea pigs to test the true specificity of the fluorescent method. Over 100 animals were used representing 102 cases. At the end of eight weeks all animals were killed and the liver, spleen, lungs and site of inoculation were examined both grossly and microscopically. There were 9 tuberculous animals, or 8.4 per cent, 6 of which were inoculated with material from advanced cases and 3 from minimal cases. This is approximately the same percentage increase as would be obtained by animal inoculation of concentrated material which is negative by the conventional Ziehl-Neelsen method. Admitting the possibility of there being a certain number of false positives even with the Ziehl-Neelsen stain, these discrepancies are never of the magnitude as found in this study. The possible explanations of such a finding are: "over-diagnosis" of slides stained by the fluorescent technique, the occurrence of relatively avirulent or nonviable tubercle bacilli and the presence of saprophytic acid-fast bacilli, especially in gastric washings. Except for the "over-diagnosis" with the fluorescent method, these same factors would apparently influence the findings with the standard stain. The authors, nevertheless, conclude that "over-diagnosis" (a term which they do not exactly define) and the relative frequency of saprophytic acid-fast bacilli in gastric contents are the most important factors for the explanation

of the lack of correlation between the sensitivity and specificity of the method. The fluorescent method, as employed, fails to correspond with the clinical, roentgenological and pathological status of the tuberculous patient too often to warrant its routine use.—*Demonstration of Tubercle Bacilli by Fluorescence Microscopy, R. J. Ritterhoff & M. G. Bowman, Am. J. Clin. Path., Technical Section, May, 1945, 9: 89.—(J. S. Woolley)*

Fluorescent Microscopy.—Fifteen hundred and three sputa were examined. Each sputum was divided between two slides; one was stained with auramine, and examined under the fluorescence microscope; the other was stained first according to Ziehl-Neelsen, then according to Hallberg. The latter method, worked out in 1939, is considered an improvement over the Ziehl-Neelsen method. Instead of carbol fuchsin, "night-blue" in carbolic acid is used, and then diluted carbol fuchsin or neutral red is applied. In all cases where no bacilli according to Ziehl-Neelsen were found, cultures were made on Löwenstein medium. Photographs of the same fields of certain slides were made which had been stained subsequently by all three methods. Fluorescence microscopy was found superior to both the other methods of staining and staining according to Hallberg gives better results than Ziehl-Neelsen. The photographic studies showed that more bacilli are stained with auramine than with the other methods. The Hallberg method is superior to Ziehl-Neelsen because the contrast conditions are better. Cultures were found superior to all the staining methods.—*On Establishing the Presence of Tuberculosis Bacilli by Means of the Fluorescence Microscope, Anna Andersson, Act. med. Scandinav., November 20, 1943, 115: 441.—(G. C. Leiner)*

Inhibiting Action of Gastric Juice on Tubercle Bacilli.—Several investigators have noted the presence of some substance in the saliva which inhibits or interferes with the growth of tubercle bacilli. Since it is almost impossible to prevent the contamination of gastric contents with saliva this inhibitory substance might act upon tubercle bacilli in such gastric contents if, for instance, the specimen is kept over night or longer, as when three-day specimens are pooled for study. The presence of some such antibacillary substance would explain the discrepancies between culture and guinea pig as reported by one observer. Other workers have found that exposure to artificial gastric juice *per se* resulted in definite inhibition or attenuation of tubercle bacilli as evidenced by the guinea pig results. One might conclude that the gastric juice alone has its own injurious effect upon tubercle bacilli. Several observers have found that gastric acidity was not usually high enough to be a serious inhibitory factor. On the other hand some writers have stated that there are no harmful substances present in gastric juice and that tubercle bacilli may be safely left in contact with gastric contents for hours or days. Working with natural gastric contents the laboratory at the Glen Lake Sanatorium has been able to show that tubercle bacilli are inhibited both in their ability to grow on culture and to infect guinea pigs in many specimens, depending largely on how fresh the specimens were. For example, a single gastric lavage was received and divided into three portions. The first portion was treated and cultured immediately. The second portion was placed in the 37°C. incubator over night and on the next day treated and cultured. The third portion was placed in the icebox for two days before being inoculated into a guinea pig. The results were as follows: (*1*) A heavy positive culture in about three weeks. (*2*) Never any growth. (*3*) No demonstrable lesions when the pig was autopsied at six weeks. Bacilli from *1* readily infected another pig, thus proving the virulence and identity of the strain. An investigation of more gastric specimens similarly treated frequently gave like results. The disagreement between culture and guinea pig, where the inoculation was delayed, was so noticeable that a new series of gastric specimens were studied in which the entire content of the lavage was treated immediately upon receipt.

A portion of the treated sediment was cultured at once and the remaining sediment placed in the icebox as before to await inoculation. In this series there was a somewhat closer agreement between guinea pig and culture. Seven gastric specimens were more carefully studied. Each specimen was divided into six portions. The first portion was treated and cultured at once, the second portion after twenty-four hours in the incubator and the third portion after twenty-four hours in the icebox. The remaining portions were each seeded with 0.01 mg. of tubercle bacilli per cc. and then treated as above. In 5 out of these 7 specimens the tubercle bacilli either present or added did not grow from the portion kept in the incubator. Various degrees of inhibition were shown with the iced portion. It is evident that holding an untreated specimen at either icebox or incubator temperature is apt to convert a positive gastric lavage into a false negative one. The inhibitory action varies from one specimen to another, but strongly active gastric contents may inhibit the growth of all the tubercle bacilli therein. Contrariwise, weakly active gastric contents, or inactive gastric contents may only partially inhibit growth or may not affect it at all. Hence, any long series will contain inactive or weakly active specimens which will give a few positive cultures regardless of the methods used to hold or store such inactive specimens. These occasionally positive cultures tend to assure the workers that all is well with their technique. The nature of the inhibitive substances or combination of substances has not yet been determined. The conclusion is that it would seem wise to treat all gastric contents for culture or animal inoculation as soon as they are received for the substances concerned in the inhibition require time. It is also apparent that higher temperatures speed the reaction. Furthermore, no time should be lost between treatment and the inoculation of media or animals. The practice of accumulating several specimens over a period of days and pooling the same should be discouraged.—*Inhibitive Effect of Gastric Lavage on Tubercle Bacilli: A Preliminary Report, V. M. Schwarting, Am. J. Clin. Path., June, 1945, 15: 234.*—(*J. S. Woolley*)

Pulmonary Lavage.—The authors have systematically replaced gastric lavage by pulmonary lavage. Two cc. of a 2 per cent pantocain solution and 20 cc. of a normal saline are installed supraglottically. After introduction of a cough reflex the expectorated liquid is examined microscopically and by culture. The results of 70 cases are presented. All patients had had negative sputa and gastric contents for at least ten months. Sixty-six were negative on pulmonary lavage and 4 positive (5 per cent of total). These comprised 2 cases with partial pneumothorax, one with an infiltrative lesion treated with rest only and one a productive bilateral lesion. Pulmonary lavage was well tolerated by all patients. No untoward effects, no fever nor hemoptysis was encountered. Ninety per cent had slight rhonchi and sibilant or crepitant râles in the bases which persisted for about three hours. The only contraindications are a decompensated heart and acute attacks of asthma. It is the authors' impression that pulmonary lavage should be substituted for gastric lavage for its easy technique as well as its better results.—*Investigacion del bacilo de Koch en el lavado del arbol respiratorio, A. P. Heudtlass, J. A. Marti & A. Adamo, Prensa méd. argent., July 13, 1945, 32: 1327.*—(*W. Swienty*)

Pulmonary Lavage.—The available methods to detect tubercle bacilli in sputum and gastric specimens are not entirely satisfactory. The detection of tubercle bacilli is particularly important in the evaluation of pulmonary shadows discovered in mass surveys. A new method has been worked out, consisting in the puncture of the trachea at the level of the crico-thyroid membrane, followed by the introduction of an anesthetic and of physiological salt solution. By assuming the Trendelenburg position, the fluid is uniformly distributed in the various segments of the lung; finally the patient is made to expectorate the injected fluid which is collected and examined on con-

centrate and culture. The author has not yet employed this method on a large scale; the preliminary results, however, seem to justify further studies. The procedure is simple and is well tolerated by the patients.—*Lavado pulmonar en el diagnostico etio-patogenetico o evolutivo de la tuberculosis, M. de Abreu, Hoja tisiol., March, 1945, 5: 83.*—(*L. Molnar*)

Acid-fast Saprophytes.—Acid-fast saprophytes occur without as well as within the human body, and they may occur in healthy as well as in sick persons. The differential diagnosis from true tubercle bacilli is very important, especially so since acid-fast saprophytes are found more commonly than is generally believed. In the author's series of 1,654 cultures, he found 10 acid-fast saprophytes which were nonpathogenic for guinea pigs, a percentage of 0.6. The percentage is similar to a much larger series by Lester who found 130 nonpathogenic acid-fast bacilli in 26,343 cultures, or 0.5 per cent. The importance of recognizing saprophytes for what they are is quite obvious. Saprophytes should be suspected if cultures are not entirely typical of tubercle bacilli, especially if the colonies are of tough consistency, and of variable colors, such has yellow-brown, yellow-red or brick-red. Also, if acid-fast cocci, or non-acid-fast rods and cocci are found in the same culture tubes, saprophytes may be suspected. Clinically, the results of cultures should be doubted if the X-ray picture, although it may be characteristic of tuberculosis, appears to be at variance with the demonstration of tubercle bacilli. Especially in cases of bronchiectasis which are otherwise typical the presence of acid-fast bacilli should not be construed to mean tuberculosis unless the bacilli are pathogenic for guinea pigs. The author has 2 cases in which the diagnosis was saccular bronchiectasis. One of these had been treated for pulmonary tuberculosis in a sanatorium. The author's 10 cases all had tuberculosis as demonstrated by X-ray and clinical picture. Three cases had active tuberculosis, 5 had probably healed tuberculosis and 2 had healed tuberculosis.—*Säurefeste Saprophyten, eine wichtige Fehlerquelle bei der Tuberkulosediagnostik, E. Hedvall, Acta med. Scandinav., 1945, 121: 71.*—(*H. Marcus*)

Hematology in Tuberculosis.—To correlate the value of hematological studies in tuberculosis with controlled experimental infections, the authors have studied four groups of guinea pigs under strictly controlled conditions. Three groups of animals had been inoculated with BCG vaccine. One group was inoculated by the multiple puncture method of Rosenthal, another by Weill-Halle's scarification method and the third by Wallgren's intracutaneous route. The fourth group remained as controls. After a determination of a base-line for all hematological values, all animals were infected with virulent human tubercle bacilli by the intraperitoneal route. Biweekly complete blood counts were done on all animals until death, or until the 103rd to 110th days, when the survivors were killed. Clinically and at autopsy the fact was again substantiated that BCG vaccination in guinea pigs is of definite value in limiting the infection and prolonging the life of the animal. Rosenthal's multiple puncture method seemed to be most efficient in this respect. The investigation of the white blood cells showed that the total white count, the differential monocyte count, the lymphocyte-monocyte ratio and the leucocytic index are of definite value as an aid in the prognosis of tuberculosis. In every case the hematological findings coincided with the clinical and autoptic observations. Briefly, the results may be summarized by stating that the higher the total white cell count, the higher the monocyte count, and the higher the monocyte lymphocyte ratio, the more unfavorable the prognosis. The variables are all combined in the leucocytic index, first proposed by Crawford and Medlar in 1935. It equals the value of the neutrophil-lymphocyte ratio plus the value of the elevation of the monocytes plus the value of the abnormal total white cells. The higher the index the worse the prognosis.—*Hematological Studies in Tuberculosis, K. Birkhaug & H. Schjelderup, Acta med. Scandinav., 1945, 121: 1.*—(*H. Marcus*).

Bronchospirometry Studies in Collapse Therapy.—In 13 patients with pulmonary tuberculosis, functional examination of the lungs was made before and after institution of pneumothorax. The second examination was made after four to six insufflations to avoid any influence on the results of a favorable or unfavorable development of the pulmonary lesions. The results so obtained are true expressions of the action of the pneumothorax. In each examination vital capacity, complemental air, supplemental air, respiratory volume, oxygen consumption and the equivalent of ventilation were determined. A comparative study was made of the relative values of these findings in both hemithoraces. An analysis of the observations shows that in the collapsed lung the bronchospirometric values diminish constantly. The reduction of the vital capacity is more accentuated than that of the respiratory volume. The decrease of the vital capacity is mostly due to the reduction of reserve air but also to the diminished complemental air. The average of this reduction was 15.2 per cent for the vital capacity; 12.4 per cent for the complemental air; 19.8 per cent for the supplemental air; 12.1 per cent for the respiratory volume. These reductions are more accentuated in pneumothorax with atelectatic lung. In certain cases the pulmonary ventilation diminishes so much that no graphic registration of the existence of supplemental and complemental air can be obtained. The oxygen consumption also shows appreciable reduction. It was most marked in partial atelectatic collapse because the pulmonary circulation is absent in atelectasis. The average for all cases was 11.6 per cent. Pinner, Leiner and Zavod have shown that collapse therapy influences more the oxygen consumption than the pulmonary ventilation. In the authors' study the reduction of the oxygen consumption was scarcely inferior to the reduction of the respiratory volume. The equivalent of ventilation improved with the institution of pneumothorax in 9 cases out of 12. It improved in the contralateral lung in 5 cases, was stationary in one and became less favorable in 5 cases. The improvement or retrogression of the equivalent of ventilation in the pneumothorax lung depends upon the existence of a selective or contraselective collapse and the complete exclusion of dead space. The authors believe that the anatomical and functional conditions of the diseased lung require of the healthy lung a better respiratory work with a low (more favorable) equivalent of ventilation. After compensatory action is no more required and function of the diseased lung has been favorably modified, the equivalent of ventilation may become higher. In collapse therapy, the vicarious function of the contralateral lung is evident. The respiratory volume was elevated in the contralateral lung in 11 cases and kept the same value in the remaining 2. The oxygen consumption was also increased in the contralateral lung in 11 cases, stayed the same in one and diminished in one case.—*Estudios broncoespirometricos en la colapsoterapia, R. F. Vaccarezza & A. Soubrié, An. Cáted. de pat. y clin. tuberc., June, 1944, 5: 5.*—(*W. Swienty*)

Pulmonary Elasticity.—Pulmonary elasticity in living man was studied on 16 patients suffering from different diseases. The method of Christie and McIntosh was used. The results obtained are presented in two tables. Table 1 shows the results on 7 patients suffering from pulmonary tuberculosis and one patient with spontaneous pneumothorax, all showing normal figures. Two patients with nonrespiratory diseases showed a quotient of pulmonary elasticity of 2 and 4 (normal 3.4 to 7.6). In table 2 the results obtained on patients with other pulmonary diseases are given. These are in accordance with those obtained by Christie and McIntosh. The procedure to determine pulmonary elasticity is simple and may help the clinician and the radiologist to depict the existence of true emphysema in borderline cases. When, in cases of emphysema, the figures are normal, this means that this is entirely functional and not anatomical and therefore reversible.—*La elasticidad pulmonar in clinica, M. R. Castex, E. S. Mazzei & G. Caputo, Arq. Inst. brasil. para investigacao da tuberc., 1941–42, 5: 17.*—(*P. B. Franca*)

"Perfect" Pneumothorax.—A perfect artificial pneumothorax performs two duties. It relaxes tension in the neighborhood of the diseased lung area allowing the diseased tissue to assume the optimum position for healing. It also immobilizes the diseased area. To insure a perfect pneumothorax, the diseased as well as the healthy lobe must be free of adhesions. If the healthy lobe is adherent, it cannot assume the function of the diseased lobe, even though the latter might be selectively collapsed. Observation of the respiratory cycle fluoroscopically shows that the selectively collapsed diseased lobe is immobilized only if the healthy lobe is free to expand over and above its natural limits and thus assume part of the function of the diseased lobe. When the entire lung is affected and no selective collapse can be expected, improvement in the patient's condition must be attributed to a selective collapse of disseminated diseased areas within the lung. The scattered lesions can take up the "slack" and internal selective relaxation and immobilization can be achieved to the degree that the diminished lung volume affords. Conversely, adhesions of the diseased areas, a "contraselective" collapse, may give the impression that the patient is not benefited by the pneumothorax. This is not entirely true, however, because the diseased lung is immobilized if the healthy lung is free of adhesions and able to take over the function of the sick lung. Relaxation is, of course, impossible under these circumstances. If the contralateral lung is free from disease, a mobile mediastinum is to be regarded as an asset because the healthy lung can then take on some of the function of the collapsed lung. By the same reasoning patients derive more benefit from pneumothorax therapy by lying on the healthy rather than on the pneumothorax side.—*The "Perfect AP", G. Day, Lancet, September 8, 1945, 249: 300.*—*(H. Marcus)*

Reinduced Pneumothorax.—The reinstitution of a pneumothorax prematurely abandoned was attempted in 10 cases. In 7 of them the pneumothorax could be reëstablished despite the fact that it had been abandoned for periods varying from three to nine months. It appears that pleural adhesions following abandonment of a pneumothorax occur less frequently than is commonly assumed.—*Le potentiél de redécollement des plèvres après cessation des insufflations de pneumothorax pendant plusieurs mois, J. Chabaud, Rev. de la tuberc., 1941, No. 5/6, 6: 366.*—*(G. Simmons)*

INDEX OF ABSTRACTS